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Prevalence and Correlates of Vaginal Estrogenization in Postmenopausal Women in the United States

Stacy Tessler Lindau, MD, MAPP¹, Annie Dude, MD, PhD², Natalia Gavrilova, PhD², Joscelyn N. Hoffmann, AB³, L. Philip Schumm, MA⁵, and Martha K. McClintock, Ph.D.^{3,4}

¹The University of Chicago, Departments of Ob/Gyn, Medicine (Geriatrics), and the Comprehensive Cancer Center, Chicago, IL

²The University of Chicago Department of Ob/Gyn

³The University of Chicago, Institute for Mind and Biology

⁴The University of Chicago Departments of Psychology and Comparative Human Development

⁵The University of Chicago Department of Public Health Sciences

Abstract

Objective—Establish current population-based vaginal estrogenization norms for postmenopausal U.S. women.

Methods—Using a U.S. national probability sample of 868 postmenopausal women ages 57 to 85 years (mean age 67.6 ± 0.3 years; 21.6 ± 0.5 years since menopause), we calculated the epithelial Maturation Value generated from self-collected vaginal specimens and compared findings with historical clinical data. Linear and logistic regression were used to describe the relationship between vaginal estrogenization and sociodemographic, physical, gynecological and sexual characteristics.

Results—Among postmenopausal women, mean Maturation Value was 46.6 ± 0.8 (SD 17.4, range 2.5–100) and stable across age groups. In every age group, vaginal estrogenization was higher among postmenopausal non-users of hormone therapy in the 2005–06 US cohort than reported for the 1960s Canadian clinical cohort. Maturation Value was also higher among women who used menopausal hormone therapy in the prior 12 months compared to those who did not (55.1 ± 1.2 vs. 44.4 ± 0.9 , $p < 0.001$). In multivariate analyses, hormone therapy use, obesity and African American race were each independently associated with higher Maturation Value. Overall, Maturation Value was not associated with sexual activity, but low Maturation Value was associated with vaginal dryness during intercourse among sexually active women.

Conclusions—Compared to 1960s clinical data, current population estimates revealed higher vaginal estrogenization across all age groups and no decline with age. The strongest independent

Corresponding author: Stacy Tessler Lindau, MD, MAPP, The University of Chicago, 5841 S. Maryland Ave., MC2050, Chicago, IL 60637, slindau@uchicago.edu, Tel: (773) 834-8986, Fax: (773) 834-5664.

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correlates of vaginal estrogenization in postmenopausal U.S. women were current hormone therapy use, obesity, and African American race. Post-menopause, half of all women exhibit low vaginal estrogenization.

Keywords

menopause; estrogenization; vagina; cytology; maturation value

INTRODUCTION

Approximately 1 in 20 postmenopausal U.S. women is a current user of estrogen therapy.¹ Estrogen therapy was first introduced in the United States for treatment of menopausal symptoms in 1899 and received US Food and Drug Administration for this use in 1941.² The annual number of dispensed prescriptions for hormone therapy grew from 16 million in 1966 to 90 million in 1999 and the prevalence of postmenopausal hormone use reached a peak of 40% among women aged 50–69 years in the late 1990s.^{1, 3–5} By 2010, due largely to public response to, and shift in medical practice resulting from, the Women's Health Initiative Study, only about 5% of menopausal women were current users.¹ Despite large shifts over the past forty years in estrogen use by menopausal women to treat vaginal atrophy, hot flushes, and other symptoms, population-based vaginal estrogenization norms have not been updated since the 1960s.

The vaginal epithelium is physiologically important to sexual function and as a barrier to infection, microbial imbalance, and environmental irritants.⁶ Menopausal decline in estrogen results in atrophy of the vaginal epithelium that can lead to genitourinary syndrome in postmenopausal women (GSM).⁷ The maturation index (MI) and the maturation value (MV), derived from microscopic evaluation of a vaginal epithelium sample, are widely used clinical measures that quantify the estrogen status of the vaginal epithelium.⁸ These measures also indicate the estrogen status of the related genital structures including the vulva, urethra and the bladder.^{9, 10} In contrast to a serum or salivary measure, a cytologic measure of vaginal epithelial maturity indicates the net effect of biologically active sex hormones (circulating levels of free estrogens, androgens, and progestogens) on the vaginal epithelium and provides an integrated measure of hormonal bioactivity over time.¹¹

Estrogenization norms were estimated in the 1960s from vaginal cytology samples from women seeking gynecologic care.^{12, 13} Although estrogen had been approved for use in the U.S. and Canada prior to the 1960s, these studies predated widespread use of exogenous estrogen. Meisels' large 1966 clinic-based study of 5920 Canadian women ages 39 to 80+ years "reported by their attending physician as being menopausal" found lower levels of vaginal estrogenization at older ages and with years since menopause.¹³ Given the large shifts in exogenous estrogen use over the past 50 years, the unprecedented aging of the population¹⁴, and emerging evidence of demographic variation in patterns of postmenopausal vulvovaginal symptoms¹⁵, updated normative data are needed.

This study uses population-based data from the 2005–6 National Social Life, Health and Aging Project (NSHAP) to establish current population norms of vaginal estrogenization in postmenopausal women and the relationship of vaginal estrogenization to

sociodemographic, health and sexual behavior characteristics. NSHAP was the first nationally-representative population-based study to collect vaginal self-swab specimens from post-menopausal women. We hypothesized that, due to greater lifetime exposure to prescription and environmental estrogens, vaginal estrogenization would be higher in a contemporary population sample as compared to Meisels' historical clinic-based sample. We also hypothesized, as previously reported by Meisels¹³ and others,⁶ that vaginal estrogenization would decline across increasing age groups and with years since menopause due to decline in endogenous estrogen production.¹⁶

METHODS

Study Population

As previously described,¹⁷ a nationally-representative probability sample of community-dwelling individuals aged 57–85 years was selected from U.S. households screened in 2004; 1550 women were interviewed between 7/05–3/06 (75.5% overall weighted response rate). Socio-economic and health characteristics of the NSHAP sample closely matched those of respondents in the 2005 Current Population Survey¹⁸ and the 2002 Health and Retirement Study.¹⁹ Anthropometric measures, health status, medication use, sexuality measures and vaginal cytology samples were obtained during in-home interviews. A self-administered vaginal swab specimen was obtained from 1,028 women (66%). Non-responders to the vaginal swab protocol were older, less likely to have graduated from high school, and less likely to report a recent pelvic examination, menopausal prescription hormone use, or frequent sexual activity in the previous year.²⁰ The Institutional Review Boards of the University of Chicago and NORC approved the protocol; all participants provided written documentation of informed consent.

Vaginal Cytology Measures

The Maturation Index (MI) quantifies the estrogen status of the vaginal epithelium and related genital structures including the vulva, urethra and bladder. Three epithelial cell types, parabasal, intermediate and superficial, are used to evaluate vaginal estrogenization. A predominance of parabasal cells (the least mature type) and absence of superficial cells indicates a low concentration of circulating estrogens (free estradiol, estrone, and estrinol). A predominance of superficial epithelial cells (the most mature type) indicates higher concentrations of circulating estrogens. Intermediate cells are moderately mature.¹¹

The self-administered vaginal swab protocol, informed by studies validating self-administration against clinical methods,²¹ and an analysis of respondent participation and sample disposition in the protocol have been previously published.^{20, 22} The MI was obtained with a complete microscopic survey and evaluation of Papanicolaou-stained vaginal squamous epithelial cell samples.²³ Coders from the McClintock Laboratory (MM and JH) experienced in hormonal cytological assessment of the rat vaginal epithelium (which closely parallels estrogen/progesterone sensitivity of the human vaginal epithelium²⁴) together with a professor of pathology and several clinical cytopathologists at the University of Chicago jointly reviewed a representative sample of slides. The teams agreed on the coding protocol. Agreement on the relative distribution of cell types

(parabasal : intermediate : superficial cells) was 100%; the exact proportion of each cell type in any given slide was identical or varied within a few percentage points (for example 5:80:15 vs 3:85:12). Coders were not asked to record cellular atypia and were blinded to all participant-level data.

Prior to coding the MI, the coder established the adequacy of each sample with a visual survey at 100× magnification of the 3 aliquots on each cytology slide. This consisted of scanning each slide systematically from left to right, checking each aliquot for cellular number, quality, and consistency, based on standard criteria.²⁵ Slides with at least 100 densely stained cells,²⁶ consistent in proportions across the three aliquots, were considered “excellent” for coding the MI. Slides were still deemed “adequate” if they had only one of the following characteristics: moderate staining, fewer than 100 cells, unstained nuclei, or cell fragments. Slides with fewer than 100 cells, faint staining and cell fragments were deemed inadequate and were excluded from this analysis. Of the 1,028 swabs collected, 869 (85.5%) were excellent or adequate for further analyses.^{20, 22} Of these, one woman had her last period during the previous year and was therefore excluded as not yet being postmenopausal, yielding a final analytic sample of 868.

The coder then recorded the proportion of parabasal (P), intermediate (I), and superficial (S) cells, combined across all three aliquots. The first analytic step was calculation of the Maturation Index (MI): the proportions of epithelial cells in each sample classified as parabasal (P), intermediate (I), and superficial (S) (%P + %I + %S = 100%; Figure 1A).²⁷

Then, to combine this information into a single score for quantifying estrogenization, the Maturation Value⁸ (MV) was calculated (Figure 1B). It is based on weighted proportions of cell types from the Maturation Index (MI) and calculated using Meisels’ formula: the percentage of superficial cells (S) plus 0.5 times the percentage of intermediate cells (I) coded from the cytology sample [$MV = \%S + (0.5 \times \%I)$].⁸ Meisels’ original study used an Estrogenization Value with slightly different cell-type weightings; superficial cells were coded as eosinophilic or cyanophilic and intermediate cells as large or small, weighting their percentages 1.0, 0.8, 0.6 and 0.5 respectively. Figure (Supplemental Digital Content 1) provides illustrative samples of vaginal self-swabs with different MV scores.

The same MV score can arise from different combinations of the three cell types: P, I and S. For example, two samples with an MI (P:I:S) of 25:25:50 and 0:75:25 each have an MV of 62.5, but the first sample reflects a higher maturation, indicated by double the percentage of fully mature superficial cells. Therefore, we also assessed the relationship between key covariates and these maturation stages: (1) early stage maturation when parabasal cells transition into intermediate cells (I + S (vs. P)) and (2) late stage maturation when intermediate cells transition into superficial cells (S (vs. (P+I))).

Years Since Menopause and Hormone Therapy (HT)

Women were asked how old they were when they had their last menstrual period. When asked in this way, 87.7% of women in the prospective Menstrual and Reproductive History Study were accurate within two years,²⁸ and in a recent study of 20 year recall, the actual and recalled ages differed by only 0.05 years.²⁹ The years elapsed since the last menstrual

period was calculated by subtracting respondent report of her age at last period (reflecting either natural or surgical menopause) from her current age. Women classified as current HT users were those whose medication log³⁰ included estrogen alone or in combination with progesterone and/or testosterone, or who self-reported use of these products in the prior 12 months. (see Table, Supplemental Digital Content 2, for a detailed description of the variables.)

Sociodemographic Characteristics

Age (used as a continuous variable in the regression models), race, Hispanic ethnicity, educational attainment and partnership status were obtained via interviewer-administered questions.

Physical Health, Gynecologic Symptoms and Sexuality

Physical health was assessed by self-report. Waist circumference (central adiposity) was measured using the National Health and Nutrition Examination Survey protocol.³¹ Body mass index (kg/m²) was calculated from direct measures of weight and height. Oophorectomy and urinary symptoms were self-reported. Samples were tested for presence of bacterial vaginosis, vaginal candidiasis and high-risk HPV using microbiology methods previously described.^{20, 22, 32} Sexual activity in the prior 12 months was defined as reporting “any mutually voluntary activity with another person that involves sexual contact, whether or not intercourse or orgasm occurs.” Sexually active women were asked whether they had trouble lubricating or pain during intercourse, two prevalent sexual concerns in this age group.³³

Statistical Methods

Means $\pm$ SEM are reported in the text. Using the same methods previously reported for analysis of the NSHAP vaginal swab data²², analyses utilized the sample weights distributed with the dataset to adjust for differential probabilities of selection and differential non-response.¹⁷ Standard errors were estimated using the linearization method, taking into account sample stratification and clustering.³⁴ All analyses were conducted using Stata Statistical Software Release 13.1 (StataCorp, College Station, TX).

Comparison to Meisels' study¹³

Between 1961 and 1965 more than 50,000 vaginal smears were collected and interpreted at the Department of Pathology of the Laval University, Quebec, Canada. Of these smears, 7354 were obtained from postmenopausal women presenting for gynecologic care. Cytohormonal analysis was performed on 5920 samples from post-menopausal women whose charts provided complete information about age, age at last menstrual period, and hormonal use for 3 months prior to the date of the cytology collection. Technically unsatisfactory smears and those with marked inflammatory changes caused by microorganisms were excluded. For each sample, an estrogenic value was estimated and mean estrogenic values were reported by five-year age group and by years since menopause.

To compare our data to the Meisels study, we computed the mean MV for the same age groups and regressed these mean values, together with those reported by Meisels, on a

continuous covariate consisting of integer values representing the age group (i.e., 55–59=1, 60–64=2, etc.). Since Meisels' study excluded women who had received HT within the past three months, all NSHAP respondents reporting current HT use or any use in the past 12 months were excluded from this comparison (NSHAP did not document the last date of use). A binary covariate distinguishing between the two studies (NSHAP versus Meisels) was included in the model, and an interaction term was used to compare the cross-sectional relationship between mean MV and age between the two studies. Each observation (representing the mean MV for a particular combination of study and age group) was weighted in proportion to the number of individuals used to compute the average. This type of aggregate analysis is common in epidemiology and other disciplines where individual-level data are not available.³⁵

Other analyses

Multiple linear regression was used to model the mean MV in the NSHAP sample as a function of the demographic, physical health and sexual covariates. A baseline model (Model 1) was first fit using age and years since menopause (both continuous) plus HT use over the last 12 months. We then added to this model race, ethnicity, education, waist circumference, bilateral salpingo-oophorectomy, and sexual activity (Model 2). Residual plots were used to check for nonlinear effects and non-constant variance, and interaction terms between age, years since last period and HT use were tested.

We also modeled separately the relationship between both the early and late stages of epithelial maturation and the covariates by fitting separate Generalized Linear Models (GLMs) to (1) the proportion of cells classified as intermediate and superficial (early stage) and (2) the proportion classified as superficial (late stage), using a logit link function with variance proportional to the binomial variance. Results are presented in Table (Supplemental Digital Content 3), with exponentiated coefficients representing the multiplicative change in the odds of being classified in the corresponding category(ies) (i.e. the odds of transitioning from the less to the more mature cell type). For both the linear and generalized linear models, the effects of age and HT were examined by plotting the average (marginal) predicted outcome by age, separately for HT users and non-users.

Logistic regression was used to examine the relationship between MV and the binary clinical and behavioral outcomes. A separate model was fit to each outcome, including maturation value, age and HT use as covariates. To facilitate interpretation, MV was first standardized by subtracting the mean and dividing by the standard deviation, so that the regression coefficient represents the change in log odds associated with a one standard deviation increase in MV (i.e., +17). Coefficients were exponentiated to yield odds ratios, which are reported together with their corresponding 95% confidence intervals.

To examine the possible bias due to differences between respondents who provided a sample adequate for analysis and those who did not, we repeated our analyses using Inverse Probability Weighting (IPW) to adjust for differential rates of item nonresponse to this measure.³⁶ Specifically, we fit a logistic regression model in which providing an adequate sample was the outcome and the factors previously reported as being associated with nonresponse for the vaginal swab (i.e., older age, less education, greater time since last

pelvic exam, no hormone use during menopause and no recent sexual activity),²⁰ plus all of the remaining covariates in Model 2 were included as predictors. The reciprocal of the predicted probabilities of providing a vaginal specimen were then multiplied by the sampling weights, and this new weight was used in place of the sampling weights.

RESULTS

The mean age of the analytic sample (range 57–85 years), including HT users and non-users, was 67.6 ± 0.3 years and mean age at menopause was 45.7 ± 0.4 (including surgical and natural menopause). Mean years since last menstrual period (LMP) was 21.6 ± 0.5 for women having both natural and surgical menopause (Table 1), and had a correlation with age of 0.67. The weighted mean age at LMP for women who did not have a premenopausal hysterectomy was 49.5 ± 0.4 years. In the prior 12 months, 46% had been sexually active (of those sexually active, 86% reported having vaginal intercourse usually or always, and 92% at least sometimes). Common gynecologic and sexual function symptoms were similar among women who agreed to provide a vaginal self-swab specimen and those who refused (Figure 2).

Among postmenopausal women, the mean MV was 46.6 ± 0.8 (SD 17.4, range 2.5–100, Figure 1B). More than a quarter (28%) had MV scores between 50 and 53, due to a predominance of intermediate cells ($89 \pm 0.6\%$, on average) among those in MV quantiles 4–6 of 9 (Figure 1A). The mean MV estimated using the IPW-adjusted weights to correct for potential non-response bias was nearly identical (46.1).

Comparison with the 1960s study

In every age group, vaginal estrogenization was higher among postmenopausal non-HT users in the 2005–06 US cohort than reported for Meisels¹³ 1960s Canadian clinical cohort of postmenopausal non-HT users seeking gynecologic care (Figure 3A). Differences in MV means between studies ranged from 5.59 ± 2.56 (95% CI = $-0.32, 11.50$) among ages 55–59 to 24.56 ± 3.25 (95% CI = $17.07, 32.05$) among ages 80+).

Factors associated with maturation value

Mean MV was also significantly higher comparing US postmenopausal women who used HT in the last 12 months to those who had not (55.1 ± 1.2 vs. 44.4 ± 0.9 , $p < 0.001$). The mean MV of women who were previous HT users (discontinued HT more than 12 months prior to the study) was indistinguishable from women who had never used HT (43.5 ± 1.0 vs. 45.1 ± 1.2 , $p = 0.21$). In a model adjusting for age and years since last menstrual period, the difference in mean MV between those who had used HT in the last year and those who had not was 10.76 (95% CI = 7.73, 13.79) (Table 2, Model 1) and was even higher (12.44, 95% CI = 9.19, 15.70) after adjusting for additional sociodemographic, physical and gynecological characteristics (Table 2, Model 2 and Figure 3B). Higher MV observed in current HT users reflected both early and late stage epithelial maturation patterns (see Table, Supplemental Digital Content 3, describing results of generalized regression models to test which stages of vaginal epithelial maturation were associated with sociodemographic, health

and sexual characteristics). There was no evidence of an interaction between age and HT use in predicting MV ($p=0.80$).

Unlike Meisels' study¹³, which found a strong negative association between MV and age, mean MV in the US population was not lower at older ages ($p = 0.005$ for a test of equivalent slopes in the two studies, Figure 3A). There was no statistically significant association between age and mean MV, either when adjusting only for HT use and years since last menstrual period (Model 1, $p = 0.93$) or when adjusting for the full set of covariates (Model 2, $p = 0.59$). In fact, with each additional decade of age, the odds of detecting superficial cells actually increased by 28% (95% CI = 4–57%, $p = 0.018$) (Table and Figure, Supplemental Digital Content 3 and 4, show (A) early stage maturation (predicted percentage of both intermediate and superficial cells) and (B) late stage maturation (only superficial cells)). In the full model, MV was not significantly associated with years since last menstrual period ($p = 0.19$), and there was no evidence of an interaction between years since last period and age ($p = 0.75$).

Although our population-based sample did not exhibit the age-related decline in MV observed by Meisels in his 1961–65 clinical cohort, the categorical distribution of MV using Meisels' criteria¹³ was nearly identical in the two samples. Comparing NSHAP to Meisels, low MV (0–49) was 50.5% and 50%, respectively; moderate MV (50–64) was 40.6% and 40%; high MV (over 65) was 8.9% and 10%. The MV range, however, was notably different. In NSHAP, MV ranged from 2.5–100; no specimens had an MV of zero (“extreme vaginal atrophy”). In Meisels' study, MV was zero for 26.7% of specimens from women ages 55–59 and 54% of specimens from women ages 80 and older. Even if we assume all of the 147 NSHAP samples classified as inadequate for our analysis were MV=0, the overall extreme vaginal atrophy rate would still be only 16.9%. In the NSHAP data, we did not see a statistically significant increase with age in the proportion of women with low MV.

Central adiposity was associated with higher MV, with each additional inch in waist circumference estimated to increase MV by 0.58 (95% CI = 0.34, 0.82) (Table 2, Model 2). Body Mass Index (BMI) was similarly associated with MV. As with HT use, adiposity was more strongly associated with early than late stage maturation (see Table, Supplemental Digital Content 3). Bilateral oophorectomy was not associated with MV, confirming that extra-gonadal tissue is the dominant source of estrogen in postmenopausal women. Both BMI and waist circumference had a weak negative correlation with age ($r = -0.10$, and -0.05 , respectively).

African American women had a higher MV than White women (difference 8.61 (95% CI = 5.09, 12.13), Table 2, Model 2), adjusting for HT use, obesity and other sociodemographic, health, gynecological and sexual factors. As with adiposity, race was more strongly associated with early than late stage maturation (see Table, Supplemental Digital Content 3).

Maturation value and gynecological and sexual conditions

MV was similar among sexually active and inactive postmenopausal women. Among sexually active women, lower MV was associated with problems lubricating ($p=0.001$), but not with pain during intercourse (Table 3).

MV was positively associated with vaginal candidiasis ($p < 0.01$), bacterial vaginosis ($p < 0.001$), as well as difficulty initiating and completing urination ($p = 0.04$), adjusting for age and HT use in the last year (Table 3). Although not shown, adjusting for sexual activity did not substantially alter the results. MV was not associated with high-risk HPV positivity or urinary incontinence.

DISCUSSION

This study is the first to establish current population-based vaginal estrogenization norms for US postmenopausal women. Confirming our hypothesis, vaginal estrogenization was higher in our 2005–06 population-based sample than in Meisels' 1966 clinical benchmark study.¹³ As expected, vaginal estrogenization was higher among current HT users as compared to others in the NSHAP sample, but even non-users appeared to be more estrogenized than women in the 1960s. Postmenopausal vaginal symptoms are commonly attributed to age-related atrophy, and we expected to confirm the prior finding that MV would decline with increasing age. However, vaginal estrogenization was found to be stable across older age groups in the US population.

We interpret the differences between our results and those of Meisels' previous study as reflecting, at least in part, the difference between a clinical cohort and a probability sample of the general population. In particular, since the clinical cohort was drawn from menopausal women seeking gynecologic care, we would expect to find a higher prevalence of extreme atrophy ($MV = 0$). While it is possible that our estimates may have some bias due to item non-response, it is unlikely that this accounts for much of the observed difference between the two studies. In NSHAP, although women in poorer overall health were less likely to provide a specimen, those with gynecological symptoms and/or sexual function concerns were more likely than others to participate,²² which would bias our findings toward an over-estimate of atrophy. Furthermore, the rate of difficulty lubricating, a prevalent symptom of vaginal atrophy, was lower among women who declined to provide a vaginal sample than among those who did (35% versus 41%). Finally, adjusting for the characteristics of women who did not provide a sample yielded similar results.

Although women in the NSHAP study did not demonstrate a declining pattern of vaginal estrogenization with age as was observed in the Meisels study, the proportion of women with low MV (50%) was about the same as reported by Meisels (1966). Consistent with this finding, 41% of women in the NSHAP population-based sample (44% of HT non-users) reported problems with lubricating and this proportion was stable across age groups. Huang and colleagues found, based on self-report, a similar prevalence of vaginal dryness (50%) in a cohort of 1,017 community-dwelling postmenopausal women, ages 55–75, recruited from a Washington State health maintenance organization database.¹⁵ The Women's Health Initiative (WHI) study, using baseline self-report data from 98,705 postmenopausal women ages 50–79, found a lower prevalence of vaginal dryness (27%), but 44% of these women (as compared to 21% of women in our study) were current users of hormone therapy. Combining symptoms of dryness and itching or irritation, the overall prevalence in the WHI cohort was 48%³⁷ and stable across postmenopausal age groups; this finding aligns with cytologic evidence from our study that vaginal estrogenization did not vary significantly

across postmenopausal age groups. Similar proportions of women experiencing vaginal dryness or vaginal discomfort (48–55%) have been reported in other studies based on surveys of postmenopausal women.^{38–40}

Adipose tissue is a principal endogenous source of estrogen in the postmenopausal woman.⁴¹ In addition to promoting estrogen synthesis, obesity has been positively associated with insulin-driven inhibition of hepatic sex hormone binding globulin (SHBG) synthesis and, therefore, higher levels of circulating free estrogens.⁴² Lukanova and colleagues, using clinical cohort data from New York and Sweden, found a positive association between measured BMI and circulating estrogens in post-menopausal women.⁴³ Liedtke and colleagues, using data from the German population-based Mammary Carcinoma Risk factor Investigation (MARIE) study of postmenopausal women, found that waist circumference was positively associated with estrogens and free testosterone, and negatively with SHBG.⁴⁴ Consistent with these findings, we find a strong, positive, independent association between obesity and vaginal estrogenization. Rates of obesity among U.S. women have increased from 15.0% in 1960 to 35% in 2012.^{45, 46} This rise in the rate of obesity may partially explain the differences in vaginal estrogenization, comparing the contemporaneous to the historical sample. Additionally, exogenous estrogen exposure via hormonal contraception (introduced in 1960 in U.S., 1969 in Canada),⁴⁷ menopausal estrogen therapy and environmental exposure⁴⁸ have grown substantially since the 1960s.

African American women exhibited higher vaginal estrogenization than white women, even after adjusting for other sociodemographic traits, HT use, obesity and other factors. This finding corroborates evidence from the U.S. Multiethnic Cohort Study showing higher free estradiol levels in African American as compared to white non-Hispanic women.⁴⁹ In 2005–06, more than 10% of the US postmenopausal population identified as African American or Black. Meisels did not report race, but 97% of the overall Canadian population identified as white in 1961.⁵⁰ The physiologic effects of exogenous environmental exposures, including differential exposure to racial discrimination and other forms of stress, in the US population may contribute to observed differences in vaginal estrogenization between Black and White women in the US and between the current and historical studies. Evidence of higher end-organ estrogenization in postmenopausal Black women warrants further study as a mechanism or cofactor of later life health and disease disparities.

Vaginal estrogenization was also independently associated with common gynecologic conditions. Higher MV was associated with yeast vaginitis as in younger women⁵¹ and women receiving HT. Unlike younger women, higher MV was also associated with bacterial vaginosis (BV), confirming the earlier finding by Cauci and colleagues that the pathophysiology of postmenopausal BV may differ from premenopause.⁵² There was no association between MV and high-risk HPV positivity, also confirming previous reports.^{53, 54}

MV was not associated with sexual activity, but, among sexually active women, lower MV was associated with trouble lubricating during intercourse. Consistent with prior studies that have found limited or no benefit to HT for alleviation of urinary symptoms in postmenopausal women,^{55–57} we did not find a significant association between vaginal

estrogenization and self-reported urinary incontinence. However, other urinary symptoms were associated with higher MV. Participation bias does not explain this finding; participation in the vaginal swab protocol was higher among women with urinary incontinence (22.8% versus 15.1% without) and other urinary symptoms (59.1% versus 50.4%). These results demonstrate that not all postmenopausal urogenital symptoms are related to low vaginal estrogen.

This population-based study used a vaginal self-swab method, including collection of two self-administered vaginal swabs that were sent first to a microbiology laboratory and then to a vaginal cytology laboratory.²⁰ We describe and address potential limitations introduced by differential non-response to the vaginal self-swab protocol and missing data from the analytic sample. Even with these stated limitations, we know of no other study that uses a population-based sample to produce postmenopausal vaginal estrogenization norms. Limitations of our sample should be weighed against limitations of historical data (now more than 50 years old) and clinical data (typically obtained from local cohorts of women presenting with gynecologic complaints).

Variation in sample collection would likely have been higher with the self-collection method as compared to the clinical protocol. However, expected relationships between MV and covariates support internal and external validity of the field methods. Methods for coding cells and calculating MV could also explain observed differences between studies. Meisels initially subcoded superficial cells as eosinophilic or cyanophilic and intermediate cells as large or small, weighting their percentages 1.0, 0.8, 0.6 and 0.5 respectively to calculate an “Estrogenic Value (EV).”¹³ In response to critiques, and describing the term as a “misnomer,” he simplified coding and calculations (all superficial cells weighted 1.0 and all intermediate cells 0.5) to create the Maturation Value,⁸ which we used here. To evaluate whether our use of MV versus Meisels’ use of EV in his 1966 paper might explain our higher MV values, we conducted a sensitivity analysis calculating the MV for the NSHAP cohort with the lowest possible weights for all superficial (0.8) and all intermediate (0.5) cells. Even after this procedure, the NSHAP cohort exhibited higher mean MV in every age group compared to the historical sample. This finding supports our conclusion that, contrary to historical clinic-based evidence, there does not appear to be an age-related decline in vaginal estrogenization after menopause. Post-menopause, half of all women will exhibit vaginal atrophy, but half will not.

Conclusions

Compared to 1960s clinical data, current population estimates revealed higher vaginal estrogenization across all age groups and no decline with age. The strongest independent correlates of vaginal estrogenization in postmenopausal U.S. women were current hormone therapy use, obesity, and African American race. The independent association of vaginal estrogenization with African American race suggests the need for research focused on physical and social environment exposures and could have implications for understanding racial disparities in estrogen-related symptoms and diseases. Clinically, this study has implications for management of genital complaints in postmenopausal women. Genitourinary syndrome of menopause,⁷ a condition associated with a decrease in estrogen,

should certainly be considered in the differential diagnosis of postmenopausal genital symptoms, such as irritation, itching and dryness. However, our findings also indicate that post-menopausal women with genital complaints should be evaluated for other inciting or co-morbid causes of genital symptoms before initiating treatment for atrophy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Distribution of (A) the Maturation Index (MI; % parabasal, % intermediate and % superficial vaginal epithelial cells = 100% cells) and (B) the Maturation Values (MV; range 2.5–100) of all 868 postmenopausal women providing excellent or adequate vaginal cytology specimens in Wave 1 (2005–6) of the National Social Life, Health and Aging Project (NSHAP; including HT users and non-users). The relative proportion of each of three cell types (A) are presented for the nine quantiles of the Maturation Value distribution (B).

Figure 2.

Proportion of respondents reporting four different genitourinary problems, separately by whether a vaginal cytology specimen was obtained (dark bars) or not (light bars). Shown are the weighted estimates together with 95% confidence intervals.

Figure 3.

A. Maturation Value (MV) of HT non-users versus age, comparing Meisels' 1961-5 clinical cohort and the nationally representative cohort from Wave 1 (2005-6) of the National Social Life, Health and Aging Project (NSHAP) (with dashed regression lines, $p = 0.005$ for testing the null hypothesis of equal slopes). Means for 5-year age groups among HT non-users are plotted with sample sizes and 95% confidence intervals only for NSHAP as neither SEM nor standard deviations were provided by Meisels.¹³

B. Comparison of HT users (solid regression line) and non-users (dashed regression line) in the NSHAP sample. Marginal means and pointwise 95% confidence intervals are based on the multiple linear regression containing age, HT use, and several socio-demographic, physical and gynecological and sexual characteristics (Model 2, Table 2).

Table 1

Characteristics of postmenopausal women providing adequate vaginal cytology specimens in Wave 1 (2005–6) of the National Social Life, Health and Aging Project (NSHAP)

Variable	Weighted mean±SD or Percent ^a	n ^b
Maturation value	46.6±17.4	868
Age (years)	67.6±7.3	868
Race (%)		867
White	84.5	
African-American	10.2	
Other	5.3	
Hispanic ethnicity (%)	7.1	863
Education (%)		868
< High school	17.0	
HS graduate	30.8	
Some college/associates	34.8	
Bachelor's or higher	17.5	
Married or cohabiting (%)	59.4	868
Sexually active in last 12 months (%)	46.0	856
Self-rated health (%)		864
Excellent/Very good	46.1	
Good	31.4	
Fair/Poor	22.5	
Waist circumference (inches)	36.5±5.9	863
Body Mass Index (kg/m ²)	29.3±6.5	841
Years since last menstrual period	21.6±10.5	799
Age of last menstrual period (LMP) ^c		
All women	45.7±8.1	799
Women having no hysterectomy before LMP	49.5±5.9	498
History of oophorectomy (%)		832
No ovaries removed	67.7	
One ovary removed	6.1	
Both ovaries removed	26.2	
HT use in last 12 months (%)	20.8	868
<i>Urogynecologic conditions</i>		
Current bacterial vaginosis (%)	23.4	778
Current yeast infection (%)	6.0	823
High-risk HPV (%)	6.0	861
Urinary incontinence (%)	59.1	842
Other urinary problems (%)	22.8	830
Pain during intercourse ^d (%)	18.0	324
Problems lubricating ^d (%)	41.0	321

^aEstimates weighted to account for unequal probabilities of selection and differential response rates.

^bNumber of observations with non-missing data for the corresponding variable.

^cFor women who reported their age at last menstrual period.

^dOnly asked of women who were sexually active within the past 12 months.

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Table 2

Multiple linear regression models of the maturation value (MV) among postmenopausal women in Wave 1 (2005–6) of the National Social Life, Health and Aging Project (NSHAP)^a

Covariate	Model 1 (n = 799)			Model 2 (n = 747)		
	Change in mean ^b	95% CI	p-value	Change in mean ^b	95% CI	p-value
<i>Socio-demographic characteristics</i>						
Age	−0.01	−0.29–0.26	0.93	0.08	−0.21–0.38	0.59
Race						
White (ref.)				–	–	–
African-American				8.61	5.09–12.13	< 0.001
Other				0.89	−4.36–6.14	0.74
Hispanic ethnicity				1.95	−2.50–6.41	0.38
Education						
< High school				−0.11	−4.54–4.33	0.96
HS graduate (ref.)				–	–	–
Some college/associates				−2.65	−5.26–0.04	0.047
Bachelor's or higher				−3.61	−8.22–1.00	0.12
<i>Physical and gynecological characteristics</i>						
Years since last menstrual period	0.18	0.02–0.34	0.025	0.10	−0.05–0.24	0.19
HT use in last 12 months	10.76	7.73–13.79	< 0.001	12.44	9.19–15.70	< 0.001
Waist circumference (inches)				0.58	0.34–0.82	< 0.001
Bilateral oophorectomy				0.91	−3.21–5.03	0.66
Sexually active in last 12 months				−0.26	−3.24–2.72	0.86

^aEstimates weighted to account for unequal probabilities of selection and differential response rates. Confidence intervals and p-values utilize design-based standard errors, taking into account the stratification and clustering in the sample design.

^bIndicates the estimated difference in average maturation value associated with a one unit increase in the covariate (or, for categorical covariates, the estimated difference between the indicated category and the referent).

Table 3

Separate logistic regression models for a series of important gynecological and sexual conditions, each regressed on a standardized maturation value (MV^a). Data from postmenopausal women ages 57–85 in Wave 1 (2005–2006) of the National Social Life, Health and Aging Project (NSHAP)^a

Condition	Mean standardized MV				
	With symptom	Without symptom	Odds ratio	95% CI	p-value
Current bacterial vaginosis	0.30	−0.05	1.54	1.26–1.88	<0.001
Current yeast infection	0.47	−0.04	1.56	1.14–2.13	0.006
Sexually active in last 12 months	−0.09	0.01	0.88	0.73–1.05	0.15
Pain during intercourse ^c	−0.34	−0.05	0.80	0.55–1.17	0.24
Problems lubricating ^c	−0.36	0.09	0.61	0.46–0.82	0.001
Urinary incontinence	0.02	−0.11	1.07	0.90–1.27	0.43
Other urinary problems	0.14	−0.08	1.24	1.01–1.51	0.039
High-risk HPV	0.05	−0.04	1.08	0.78–1.51	0.63

^aMaturation value standardized by subtracting the sample mean and dividing by the sample standard deviation. All models include age and HT use in the last 12 months as covariates. Estimates weighted to account for unequal probabilities of selection and differential response rates. Confidence intervals and p-values utilize design-based standard errors, taking into account the stratification and clustering in the sample design.

^bSample size differs slightly between models due to missing data for certain outcomes.

^cOnly asked of women who were sexually active within the past 12 months.