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Obesity and Reproductive Hormone Levels in the Transition to Menopause

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Abstract

Objective—To estimate associations of obesity with reproductive hormone levels as women progress from premenopausal to postmenopausal status.

Methods—This is a longitudinal study conducted in the population-based Penn Ovarian Aging Cohort (N=436). At cohort enrollment, the women were premenopausal, ages 35–47 years, with equal numbers of African Americans and Caucasians. Anthropometric measures, menopausal status and reproductive hormone measures were evaluated for 12 years. Associations of the anthropometric measures with estradiol, FSH and inhibin b in the menopausal transition were estimated using generalized linear regression models for repeated measures.

Results—Associations between obesity and hormone levels differed by menopausal status as indicated by significant interactions between each hormone and menopausal stage. Premenopausal obese and overweight women had significantly lower estradiol levels compared to non-obese women, independent of age, race and smoking (obese: 32.8 pg/mL; 95% CI: 30.6. 35.2 versus non-obese: 39.8 pg/mL; 95% CI: 37.0, 42.8, P<0.001). The associations reversed postmenopause, with obese women having the highest estradiol levels (obese: 20.6 pg/mL; 95% CI: 17.2, 24.7 versus non-obese: 12.2 pg/mL; 95% CI: 10.1, 14.8, P<0.001). Inhibin b levels were significantly lower in premenopausal obese compared to non-obese women but reversed in the late transition stage. FSH levels were lowest in postmenopausal obese compared to non-obese women (P<0.001). Measures of waist circumference (central adiposity) and waist/hip ratio paralleled the BMI results.

Conclusion—Obesity is an important factor in hormone dynamics independent of age, race and smoking in mid-life women, although the mechanisms remain unclear.

INTRODUCTION

Obesity is identified as an important modifier of reproductive hormones. In mid-life women, obesity is associated with menstrual cycle alterations, anovulatory cycles ending with bleeding, menopausal symptoms including hot flashes, poor sleep, aches and joint pain, urinary symptoms and quality of life.[1–15] Many women experience weight gain, increases in central adiposity and other changes in body composition around menopause, but the extent to which

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these changes are specific to levels or changes in reproductive hormones or to other behavioral and disease factors are complex and not clearly identified.[16–17]

While studies have reported associations between obesity and reproductive hormones, findings are inconsistent, and mechanisms that underlie these associations are unclear. For example, some studies documented a significant effect of BMI on estradiol levels, while others did not.[15, 18] Obesity was associated with an earlier age at menopause in one study but a later age at menopause in another.[19, 20] Estradiol levels were higher in postmenopausal obese women,[21, 22] but an inverse association of BMI with estradiol and inhibin b was observed in *premenopausal* obese women.[11, 15, 23] Reasons for the lower levels of estradiol in premenopausal obese women are not well understood. Moreover, there is little information on the associations between obesity and reproductive hormones as mid-life women progress from premenopausal to postmenopausal status.

In our population-based cohort, we have consistently found that body size as measured by body mass index (BMI) is an important mediator of hormone levels in the menopausal transition.[12–14] For example, women with higher BMI were more likely to enter the earliest transition stage, although less likely to reach the postmenopausal stage compared to those with lower BMI.[24] Obese women had lower levels of anti-mullerian hormone (AMH) compared to non-obese women, although antral follicle count did not differ by body size.[14, 23] Observed racial differences in mean levels of estradiol in the menopausal transition were strongly mediated by BMI [12] However, the complex associations among BMI, menopausal stage, time and other modifiers with hormone levels make it difficult to disintangle the independent contributions of BMI in these studies.

The objective of this study was to estimate associations between obesity and reproductive hormone levels at multiple time points as women progressed through the menopausal transition. Based on our previous observations,[12–14, 23] we hypothesized that obese women have lower estradiol levels, lower inhibin b levels, and higher FSH levels compared to non-obese women in the earliest stages of the menopausal transition and postmenopausal obese women have higher estradiol levels compared to non-obese women. The associations between obesity and hormones reverse in the transition stages.

METHODS

Cohort Participants

All participants in the Penn Ovarian Aging cohort (N=436) were included in this study, which was conducted over a 12-year interval from 1995 to 2007. The cohort was identified by random-digit dialing to households in Philadelphia County, Pennsylvania as described in previous reports.[14] Sampling was stratified to obtain equal numbers of African American and Caucasian women (N=218 in each group) to determine associations of race in ovarian aging. The Institutional Review Board of the University of Pennsylvania approved the study, and written informed consent was obtained from all participants.

At enrollment in the cohort, the participants were ages were 35–47 years, were premenopausal with regular menstrual cycles in normal range (22–35 days) for the previous three cycles, had an intact uterus and at least one ovary. Exclusion criteria included current use of psychotropic or hormonal medications including hormonal contraception and hormone therapies; pregnancy or breast feeding; serious health problems known to compromise ovarian function such as diabetes mellitus, liver disease, breast or endometrial cancer, and alcohol or drug abuse in the past year.

During the 12-year interval, 137 subjects discontinued. There were no significant differences in the variables of this study compared at baseline between the participants who continued throughout the study and the discontinuers (Table 1). We previously found no substantial differences between the discontinuers and active participants in a study of discontinuation in the first 5 years of the project and concluded that discontinuation was spread equally across study characteristics.[25]

Study Design

Twelve assessment periods were conducted in the 12-year interval. The first 6 periods were at approximately 8–9 month intervals, and the remaining periods were at annual intervals with a 2-year gap between periods 10 and 11. Blood samples for the hormone assessments were obtained in each assessment period in the early follicular phase (days 1–6 of the menstrual cycle) in two consecutive menstrual cycles or one month apart in non-cycling women (yielding a possible maximum of 24 hormone samples per participant).

The study was described to the participants as a general women's health study. At each assessment period, trained research interviewers obtained the blood samples, anthropometric measures and all other study data in individual in-person interviews at the participants' homes. A structured interview questionnaire focused on overall health, and participants completed a set of validated self-report measures to assess health and other variables of the study.

Study Variables

Hormones—Estradiol and follicle stimulating hormone (FSH) were measured by radioimmunoassay in the Translational Clinical Research Center of the University of Pennsylvania using Coat-A-Count commercial kits (Diagnostic Products, Los Angeles, CA). All assays were performed in duplicate, with the means of the duplicates used in analysis. The inter- and intra assay coefficients of variation were less than 5% for estradiol and FSH. Inhibin b was measured by ELISA using the commercial kit from Diagnostic Systems Laboratories (Webster, TX). The sensitivity of the assay was 7 pg/mL (range 5–531 pg/mL). The inter and intra coefficients of variation were <5% and 7.3%, respectively. For the first 10 assessment periods, Dr. Patrick Sluss, PhD, Massachusetts General Hospital, Boston performed the inhibin b assays with a solid-phase sandwich ELISA (Diagnostic Systems Laboratories, Inc., Beckman Coulter, Houston, TX) based on the use of plates coated with a monoclonal antibody specific for the alpha-subunit for detection.[26, 27] The limit of measurement for the assay was 15 pg/mL (CV=20%). The assay was controlled in triplicate using samples with mean concentrations of 155.3, 316.3, and 919.3 pg/mL, with interassay CVs of 11.6, 7.6 and 9.7%, respectively. The reference ranges for normally cycling women, follicular phase are 64 to 146 pg/mL; normally cycling women, mid-cycle: 47 to 169 pg/mL; normally cycling women, luteal phase: <15 to 72 pg/mL; postmenopausal women not on hormone therapy:<15 pg/mL. In this report, values below the sensitivity threshold (15 pg/mL) were given the threshold value.

Anthropometric measures—Measures of height, weight, waist and hip circumferences were made and recorded in duplicate at each assessment period. The average value at each period was used in analysis. Height (without shoes) was measured to the nearest 0.25 inch with a vertical tape. Body weight (in light clothing) was measured to the nearest pound. Waist circumference was measured at the level of the narrowest part of the torso as seen from the anterior aspect. Hip circumference was measured at the maximal protrusion of the hips at the level of the symphysis pubis to the nearest 0.25 inch. BMI (kg/m2) was calculated as weight (kg) divided by the square of height (cm), using the average of the duplicate measures. Metric conversions for the analysis were computer-generated. Standard cut points for three measures of adiposity were used in the analysis: BMI <25, >=25 to <30, >=30; waist circumference (WC): <80, >=80 cm; waist/hip ratio (WHR): <0.80, 0.80 to <0.85, >=0.85.

Menopausal stage—Participants were assigned to menopausal stage at each assessment period. Menopausal stage was identified using the menstrual dates at each study visit (conducted within 6 days of bleeding) and the two previous menstrual dates reported at each visit. Other confirmatory data were provided by daily diaries that participants recorded for one menstrual cycle at each assessment period, the reported number of menstrual periods between assessments, cycle length and number of bleeding days.

The definitions of menopausal stage were adapted from the Stages of Reproductive Aging Workshop (STRAW) and divided the early transition stage to better capture early transition changes.[28] We previously demonstrated significant associations between each of these stages and reproductive hormone changes.[12,13] The 5 stages in this report were: **1) premenopausal:** regular menstrual cycles in the 22–35 day range; **2) late premenopausal:** a change in cycle length of >=7 days either direction from the participant's personal baseline at enrollment in the cohort and observed for at least one menstrual cycle in the study; **3) early transition:** changes in cycle length of >=7 days either direction from the participant's personal baseline at enrollment in the cohort observed for at least two consecutive menstrual cycles in the study to 60 days amenorrhea; **4) late transition:** 90 days to 11 months amenorrhea; **5) postmenopausal**: >=12 months amenorrhea excluding hysterectomy.

Other covariates—Age at enrollment, race (African American or Caucasian), current smoking (yes, no), number of children and age at menarche were obtained in the study interviews and selected for this report based on their significance in previous reports and the goals of this study.

Statistical Analysis

The statistical analyses used general linear mixed effects regression models for repeated measures to estimate associations of each anthropometric measure with each hormone. These extensions of linear regression address among-women associations, while taking into account the longitudinal data collection. We first examined the unadjusted associations of each study variable with each hormone. We then examined the anthropometric measures simultaneously with all covariates that had an adjusted association at $P<0.15$ in multivariable models to estimate independent associations of the anthropometric measures with each hormone. The 3-way and 2-way interactions among each anthropometric measure, menopausal stage and race were included in the hormone models, each variable was adjusted for all other variables in the model. The same set of covariates was modeled for each hormone, and the final models retained all covariates and the interaction between the anthropometric measure and menopausal stage.

The hormone measures were transformed to natural log values to accommodate assumptions of the statistical models. The mean of the two hormone measurements for each subject at each assessment period was used in analysis. In cases where two hormone values were not obtained in an assessment period, the single value was used. Mean hormone values are expressed as the geometric mean (back-transformed from the natural log values) with 95% confidence intervals.

All available data at each assessment period for the 436 participants were included in the repeated measures models. Observations of pregnancy, breast feeding, and hormone use were censored at the times of their occurrence. Hormone measurements taken after a participant reported hysterectomy or cancer treatment were set to missing from the time of occurrence forward. In all models, variance estimates for the statistical tests on the regression coefficients were adjusted for the repeated observations from each participant using generalized estimating equations.[29] The significance level for the within-group comparisons at each menopausal stage was lowered to $P=0.003$ utilizing the Bonferroni correction for multiple comparisons. Comparisons of baseline variables between study continuers and discontinuers used two-sample t tests or Pearson chi square tests of association as appropriate for the distributions of

the data. All analyses were conducted using the SAS V9.13 statistical package (SAS Institute, Cary, NC). Statistical tests were two-tailed with P values <=0.05 considered significant.

RESULTS

Participant characteristics at baseline are shown in Table 1. The mean age was 41.4 (SD 3.5) years and all women were premenopausal. At Assessment Period 12, the mean age was 51.6 (SD 3.4) years; three women (1%) were premenopausal, 48% were in transition, 45% were postmenopausal and 6% had a hysterectomy.

Table 2 shows the unadjusted associations of the study variables with each hormone over the study interval. The obese women had significantly lower estradiol levels compared to non-obese women on each anthropometric measure (P<0.001). The obese women also had significantly lower inhibin b levels (P<0.001) and higher FSH levels (P<0.001) on average compared to non-obese women.

Smoking, menopausal stage and age were significantly associated with each hormone in unadjusted analysis. Race, age at menarche and number of children were not associated with the hormone levels in unadjusted analysis (Table 2).

Race and hormone levels

There were no statistically significant 3-way interactions of race, BMI and menopausal stage for estradiol, FSH or inhibin b. A 2-way interaction of race and BMI was observed only for estradiol and indicated that associations of BMI with estradiol marginally differed by race (P=0.040). African American women in the normal BMI group had lower estradiol levels on average compared to the Caucasian women (28.1 pg/mL, 95% CI: 25.0, 31.5 and 33.7 pg/mL, 95% CI: 30.3, 35.3, respectively. There was no significant interaction of race and BMI for FSH or inhibin b, and there were no significant interactions of race with the other anthropometric measures.

BMI and hormone levels

We estimated the association of BMI with each hormone in a multivariable model that included menopausal stage, smoking, age, race and the interactions of BMI with menopausal stage and race. The significant interaction (P<0.001) depicted in Figure 1A indicated that the associations of BMI with estradiol differed by menopausal stage. In the premenopausal stage, estradiol levels were significantly *lower* in the obese and the overweight groups compared to the normal BMI group (obese: 32.8 pg/mL; 95% CI: 30.6, 35.2; overweight: 34.4 pg/mL; 95% CI: 32.0, 36.9; normal: 39.8 pg/mL; 95% CI: 37.0, 42.8; P<0.001 for each comparison). In the late transition stage, estradiol levels converged and then switched postmenopause, with the lowest estradiol levels in the normal-weight group and the highest estradiol levels in the obese group (12.2 pg/mL; 95% CI: 10.1, 14.8 versus 20.6 pg/mL; 95% CI: 17.2, 24.7; P<0.001).

Figure 1B shows that the associations of BMI with FSH levels significantly differed postmenopause, when the obese group had the lowest FSH levels and the normal-weight group the highest FSH levels (Obese: 42.0 mIU/mL, 95% CI: 36.9, 47.9; overweight: 57.2 mIU/mL, 95% CI: 47.7, 68.8; normal weight: 59.3 mIU/mL, 95% CI: 50.6, 69.5). (Interaction P=0.008; obese vs normal P<0.001; overweight vs normal P=0.007).

Figure 1C indicates that the associations of BMI with inhibin b levels differed by menopausal stage, as indicated by the significant interaction (P=0.004). Inhibin b levels were significantly *lower* in the obese and overweight groups at the premenopausal and late premenopausal stages but switched in the late transition stage when the normal-weight BMI group had the lowest inhibin b levels and the obese group had the highest inhibin b levels (interaction P=0.004,

shown in Figure 1C). Postmenopause inhibin b levels were below the limit of detection for many women regardless of weight status.

Waist circumference (WC) and hormone levels

Figure 2 shows the results for waist circumference, a measure of central adiposity, which paralleled the BMI results. The association of WC with estradiol differed by menopausal stage, as indicated by the significant interaction (P<0.001). Premenopause estradiol levels on average were significantly *lower* in the obese (high) WC group compared to the low WC group (P<0.001), while postmenopause estradiol levels were significantly *higher* in the obese WC group compared to the low WC group (P=0.002).

FSH levels in the WC groups diverged at the late transition stage (interaction P<0.001). Postmenopause, the obese group had the lowest FSH levels (47.2 mIU/mL, 95% CI 42.4, 52.5) compared to the non-obese group (61.1, 95% CI 51.8, 72.1, P=0.005).

Premenopausal inhibin b levels were significantly lower on average in the obese (high) WC group compared to the non-obese group (60.4 ng/mL, 95% CI 56.8, 64.3 and 72.5 ng/mL, 95% CI 67.4, 78.0, respectively, P<0.001. Postmenopause, the mean inhibin b levels approached the limit of detection; there was no significant interaction.

Waist/hip ratio (WHR) and hormone levels

The results for waist hip ratio (WHR), a measure of visceral fat, were consistent with the BMI and WC measures. Premenopausal estradiol levels were significantly lower in the obese (high) WHR group compared to the low WHR group (37.9 pg/mL, 95% CI 35.5, 40.3 and WHR 37.8 pg/mL, 95% CI 31.4, 35.9, respectively, P=0.003). The estradiol associations reversed in the late transition; the postmenopausal obese group had the highest estradiol levels and the lowest WHR group had the lowest estradiol levels, but differences did not reach statistical significance. The interaction of WHR and menopausal stage did not reach significance (P=0.096).

The association between WHR and FSH levels differed by menopausal stage (interaction P=0.005). Postmenopause, the obese (high) WHR group had the lowest FSH levels and the low WHR group had the highest FSH levels (46.7 mIU/mL, 95% CI 40.9, 53.3 and 58.6, 95% CI: 50.9, 67.4, respectively, P=0.009).

The association between WHR and inhibin b levels differed in the premenopausal women. Premenopausal inhibin b levels were significantly lower in the obese (high WHR) group compared to the low WHR group (P=0.003) and were also higher in the overweight group compared to the normal WHR group (59.3 ng/mL, 95% CI: 54.5, 64.6; 63.2 ng/mL, 95% CI: 58.9, 67.8; and 68.9 ng/mL, 95% CI: 64.4, 73.7, respectively). Postmenopause, the majority of women had non-detectable inhibin b levels; there was no significant interaction.

DISCUSSION

This study examined associations between obesity and reproductive hormones as women progressed from premenopausal to postmenopausal status. By examining women at multiple time points over a 12-year period, the findings provide novel information about these associations over the menopausal transition. Obese premenopausal women had significantly lower estradiol and inhibin levels than non-obese premenopausal women. The associations between obesity and hormones reversed in the transition stages, and, following menopause, obese women had significantly higher estradiol levels compared to non-obese women.

The results also clearly indicate that obesity is associated with hormone levels independent of other factors known to influence reproductive hormones such as age, race and smoking status. We suspect that the change in association between estradiol levels and menopausal status is principally related to the source of estrogen production. The positive association of BMI and estradiol in *post*menopausal obese women is consistent with the well-recognized changes in estrogen metabolism that occur with ovarian senescence, when the contribution of estradiol from fat becomes dominant and obese women have higher estradiol levels than non-obese women. However, less is known about the inverse association of BMI with estradiol and the lower levels of inhibin b in *premenopausal* obese women.[11, 13, 21]

While these results confirm and further extend previous observations of a negative association between estradiol and BMI in premenopausal women,[15, 21, 23] the mechanisms for this association remain unclear. Possibly the low levels of sex hormone-binding globulin (SHBG) in obese premenopausal women, which are positively correlated with estradiol levels,[30, 31] result in greater clearance and consequently lower levels of estradiol. After menopause, when the ovarian contribution of estrogen is negligible, the higher levels of estrogen in obese women may be attributed to the contribution from the conversion of androgens to estrogens by aromatase in adipose tissue.

It is hypothesized that the association between obesity and hormones is related to insulin resistance or to other adipose-derived substances such as adiponectin or leptin.[32, 33] However, measures of insulin sensitivity did not relate to reproductive hormones in obese women in the menopausal transition, suggesting that BMI may influence reproductive hormones apart from its relationship with the metabolic syndrome.[11]

It is possible that obesity has a negative effect on granulosa cell function, and therefore decreases inhibin b levels. This would explain the negative association between inhibin b and BMI, which becomes less evident as follicles become depleted with advancing menopausal stage. Given that inhibin is a direct product of the ovary, it should become undetectable regardless of BMI in postmenopausal women, as we observed. The interaction between BMI and menopausal stage indicates that the decline of inhibin b differs between obese and thin women, but this may simply be that the thin women have higher inhibin b levels at the premenopausal baseline.

The inverse associations of inhibin b and estradiol with BMI in premenopausal women suggest that obese women may experience an earlier decline in ovarian reserve compared to non-obese women. However, the FSH levels do not support this hypothesis. Increased body size in this cohort and other studies is associated with low FSH levels, and FSH levels are similar in obese and non-obese women as they enter the menopausal transition.[12, 15, 21] Furthermore, we conducted a study of effects of body size on ovarian reserve and found no difference in antral follicle count by body size, although anti-mullerian hormone levels were lower in obese compared to non-obese women, consistent with the observations of inhibin b in the present report.[23]

Race does not appear to be a strong factor in the differential hormone levels of this study after adjusting for body size. Only estradiol had a racial association with menopausal status and this was observed only in the *premenopausal* stage, when the non-obese African American women had significantly lower estradiol levels compared to the Caucasian women. There was no racial difference in the subsequent menopausal transition stages in the adjusted models. We know of no explanation for the lower estradiol levels in premenopausal African American women but speculate that differences in body composition and lean body mass may be contributing factors.

The study included three measures of adiposity, because there is lack of agreement on the measure that best identifies relationships between body fat and hormone dynamics. From

diverse reports, it appears that BMI is a strong measure of associations with reproductive hormones, but that the strength of the measurement may vary with the specific objectives of the study and characteristics of the sample. In the present study, BMI had the strongest associations with reproductive hormones; waist circumference as a global measure of central fat paralleled the BMI results; waist/hip ratio, a measure of body shape and abdominal visceral fat, was a weaker measure, particularly after adjustment in multivariable analyses. These findings are consistent with the WISE study, where BMI and waist circumference were significantly associated with estrogens in postmenopausal women, and the highest estradiol levels were observed in obese women with large waists.[34] Abdominal adiposity measured by computed tomography scan was highly correlated with BMI, subcutaneous adiposity and visceral adiposity in the SWAN study.[35] Another study of associations between obesity and reproductive hormones utilized BMI and dual-energy X-ray absorptiometry scans but determined that the scans provided no further information than that obtained with BMI.[36] In contrast, studies of the elderly that examined adiposity and related risk factors found that waist circumference and waist-hip ratio but *not* BMI were predictors of cardiovascular and mortality risks.[37, 38]

Several limitations are considered. The hormones were measured in the early follicular phase, which is believed to be most reliable, but do not address the dynamics of the full menstrual cycle. Because estrone levels are expected to be higher in obese women due to the peripheral conversion of androgen, our findings might be even stronger if we measured estrone in addition to estradiol. Obesity may be associated with other hormones such as testosterone or SHBG that were not included in this study.[36, 39] It is possible that results could be biased by discontinuation in the cohort over the 12-year follow-up period, although this is not supported by the evidence, which showed that missing data were missing at random and were assumed to be non-differential with respect to the outcome. The study evaluated generally healthy African American and Caucasian women with no current hormone use and may not be generalizable to all menopausal women.

The strengths of this study include multiple assessments over a long time period in a population-based cohort, a clearly defined premenopausal baseline from which the women progressed through the menopausal transition, with concomitant hormone and anthropometric measures.

CONCLUSION

The findings clearly indicate that obesity in an important factor in hormone changes of the menopausal transition independent of age, race and smoking. The novel findings are important for better understanding the physiologic changes that occur during the menopausal transition. The findings also indicate that the effects of obesity should be considered when interpreting hormone levels of mid-life women, although it is important to recognize that group differences in mean hormone levels have limited clinical utility for individual patients. In menopause management, it is well-recognized that the large variability in hormone levels between and within women constrains the information that can be gained from individual hormone measures, but that increased understanding of the physiologic changes is an important tool for guiding symptom management.

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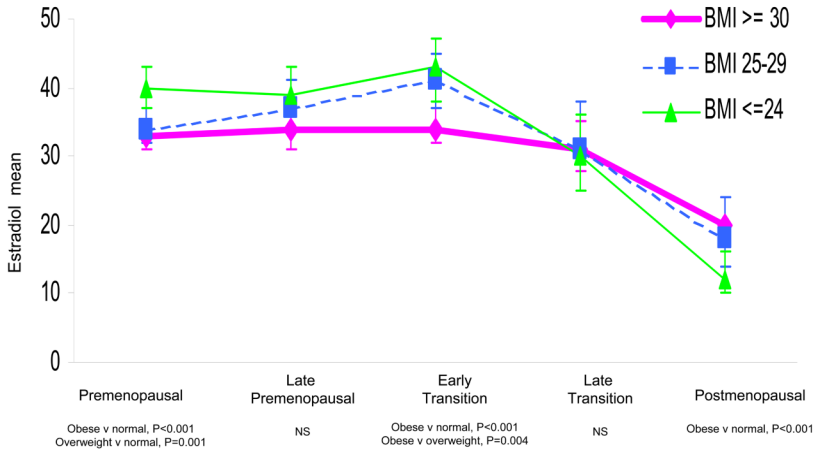
References

1. Santoro N, Lasley B, McConnell D, et al. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) Daily Hormone Study. J Clin Endocrinol Metab 2004;89:2622–2631. [PubMed: 15181033]
2. Thurston RC, Sowers MR, Chang Y, et al. Adiposity and reporting of vasomotor symptoms among midlife women: the study of women's health across the nation. Am J Epidemiol 2008;167:78–85. [PubMed: 17881385]
3. Schilling C, Gallicchio L, Miller SR, Langenberg P, Zacur H, Flaws JA. Relation of body mass and sex steroid hormone levels to hot flushes in a sample of mid-life women. Climacteric 2007;10:27–37. [PubMed: 17364602]
4. Mishra GD, Hardy R, Cardozo L, Kuh D. Body weight through adult life and risk of urinary incontinence in middle-aged women: results from a British prospective cohort. Int J Obes (Lond) 2008;32:1415–1422. [PubMed: 18626483]
5. Whiteman MK, Staropoli CA, Langenberg PW, McCarter RJ, Kjerulff KH, Flaws JA. Smoking, body mass, and hot flashes in midlife women. Obstet Gynecol 2003;101:264–272. [PubMed: 12576249]
6. Szoeke CE, Cicuttini FM, Guthrie JR, Dennerstein L. The relationship of reports of aches and joint pains to the menopausal transition: a longitudinal study. Climacteric 2008;11:55–62. [PubMed: 18202965]
7. Castelo-Branco C, Palacios S, Ferrer-Barriendos J, et al. Impact of anthropometric parameters on quality of life during menopause. Fertil Steril. 2008 Nov 1; [Epub ahead of print].
8. Thurston RC, Sowers MR, Sternfeld B, et al. Gains in body fat and vasomotor symptom reporting over the menopausal transition: the study of women's health across the nation. Am J Epidemiol 2009;170:766–774. [PubMed: 19675142]
9. Freeman EW, Sammel MD, Lin H, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. Obstet Gynecol 2007;110:230–240. [PubMed: 17666595]
10. Gopal M, Sammel MD, Arya LA, Freeman EW, Lin H, Gracia C. Association of change in estradiol to lower urinary tract symptoms during the menopausal transition. Obstet Gynecol 2008;112:1045–1052. [PubMed: 18978104]
11. Santoro N, Crawford SL, Lasley WL, et al. Factors related to declining luteal function in women during the menopausal transition. J Clin Endocrinol Metab 2008;93:1711–1721. [PubMed: 18285413]
12. Freeman EW, Sammel MD, Gracia CR, et al. Follicular phase hormone levels and menstrual bleeding status in the approach to menopause. Fertil Steril 2005;83:383–392. [PubMed: 15705379]
13. Gracia CR, Freeman EW, Sammel MD, Lin H, Nelson DB. The relationship between obesity and race on inhibin B during the menopause transition. Menopause 2005;12:559–566. [PubMed: 16145310]
14. Freeman EW, Gracia CR, Sammel MD, Lin H, Lim LC, Strauss JF 3rd. Association of anti-mullerian hormone levels with obesity in late reproductive-age women. Fertil Steril 2007;87:101–106. [PubMed: 17109858]
15. Randolph JF Jr, Sowers M, Gold EB, et al. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. J Clin Endocrinol Metab 2003;88:1516–1522. [PubMed: 12679432]
16. Donato GB, Fuchs SC, Oppermann K, Bastos C, Spritzer PM. Association between menopause status and central adiposity measured at different cutoffs of waist circumference and waist-to-hip ratio. Menopause 2006;13:280–285. [PubMed: 16645541]
17. Hong SC, Yoo SW, Cho GJ, et al. Correlation between estrogens and serum adipocytokines in premenopausal and postmenopausal women. Menopause 2007;14:835–840. [PubMed: 17667144]
18. Burger HG, Dudley EC, Hopper JL, et al. Prospectively measured levels of serum follicle-stimulating hormone, estradiol, and the dimeric inhibins during the menopausal transition in a population-based cohort of women. J Clin Endocrinol Metab 1999;84:4025–4030. [PubMed: 10566644]

19. Kato I, Toniolo P, Akhmedkhanov A, Koenig KL, Shore R, Zeleniuch-Jacquotte A. Prospective study of factors influencing the onset of natural menopause. J Clin Epidemiol 1998;51:1271–1276. [PubMed: 10086819]
20. Palmer JR, Rosenberg L, Wise LA, Horton NJ, Adams-Campbell LL. Onset of natural menopause in African American women. Am J Public Health 2003;93:299–306. [PubMed: 12554590]
21. Randolph JF Jr, Sowers M, Bondarenko IV, Harlow SD, Luborsky JL, Little RJ. Change in estradiol and follicle-stimulating hormone across the early menopausal transition: effects of ethnicity and age. J Clin Endocrinol Metab 2004;89:1555–1561. [PubMed: 15070912]
22. Lukanova A, Lundin E, Zeleniuch-Jacquotte A, et al. Body mass index, circulating levels of sex-steroid hormones, IGF-I and IGF-binding protein-3: a cross-sectional study in healthy women. Eur J Endocrinol 2004;150:161–71. [PubMed: 14763914]
23. Su HI, Sammel MD, Freeman EW, Lin H, DeBlasis T, Gracia CR. Body size affects measures of ovarian reserve in late reproductive age women. Menopause 2008;15:857–861. [PubMed: 18427357]
24. Sammel MD, Freeman EW, Liu Z, Lin H, Guo W. Factors that influence entry into stages of the menopausal transition. Menopause. 2009 Jun 6; [Epub ahead of print].
25. Nelson DB, Sammel MD, Freeman EW, Liu L, Langan E, Gracia CR. Predicting participation in prospective studies of ovarian aging. Menopause 2004;11:543–548. [PubMed: 15356407]
26. Pitteloud N, Dwyer AA, DeCruz S, et al. The relative role of gonadal sex steroids and gonadotropin-releasing hormone pulse frequency in the regulation of follicle-stimulating hormone secretion in men. J Clin Endocrinol Metab 2008;93:2686–2692. [PubMed: 18445673]
27. Welt CK, Taylor AE, Fox J, Messerlian GM, Adams JM, Schneyer AL. Follicular arrest in polycystic ovary syndrome is associated with deficient inhibin A and B biosynthesis. J Clin Endocrinol Metab 2005;90:5582–5587. [PubMed: 16030174]
28. Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Fertil Steril 2001;76:874–878. [PubMed: 11704104]
29. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
30. Akin F, Bastemir M, Alkis E, Kaptanoglu B. Associations between sex hormone binding globulin and metabolic syndrome parameters in premenopausal obese women. Indian J Med Sci 2008;62:407–415. [PubMed: 19008614]
31. Pasquali R, Vicennati V, Beertazzo D, et al. Determinants of sex hormone-binding globulin blood concentrations in premenopuasal and postmenopausal women with different estrogen status. Metabolism 1997;46:5–9. [PubMed: 9005961]
32. Garaulet M, Pérez-Llamas F, Baraza JC, et al. Body fat distribution in pre-and post-menopausal women: metabolic and anthropometric variables. J Nutr Health Aging 2002;6:123–126. [PubMed: 12166365]
33. De Pergola G, Maldera S, Tartagni M, Pannacciulli N, Loverro G, Giorgino R. Inhibitory effect of obesity on gonadotropin, estradiol, and inhibin B levels in fertile women. Obesity (Silver Spring) 2006;14:1954–1960. [PubMed: 17135611]
34. Olson MB, Shaw LJ, Kaizar EE, et al. Obesity distribution and reproductive hormone levels in women: a report from the NHLBI-sponsored WISE Study. J Womens Health (Larchmt) 2006;15:836–842. [PubMed: 16999639]
35. Thurston RC, Sowers MR, Sutton-Tyrrell K, et al. Abdominal adiposity and hot flashes among midlife women. Menopause 2008;15:429–434. [PubMed: 18204407]
36. Mahabir S, Baer DJ, Johnson LL, et al. Usefulness of body mass index as a sufficient adiposity measurement for sex hormone concentration associations in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2006;15:2502–2507. [PubMed: 17164376]
37. Dobbelsteyn CJ, Joffres MR, MacLean DR, Flowerdew G. A comparative evaluation of waist circumference, waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. The Canadian Heart Health Surveys. Int J Obes Relat Metab Disord 2001;25:652–661. [PubMed: 11360147]
38. Price GM, Uauy R, Breeze E, Bulpitt CJ, Fletcher AE. Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. Am J Clin Nutr 2006;84:449–460. [PubMed: 16895897]

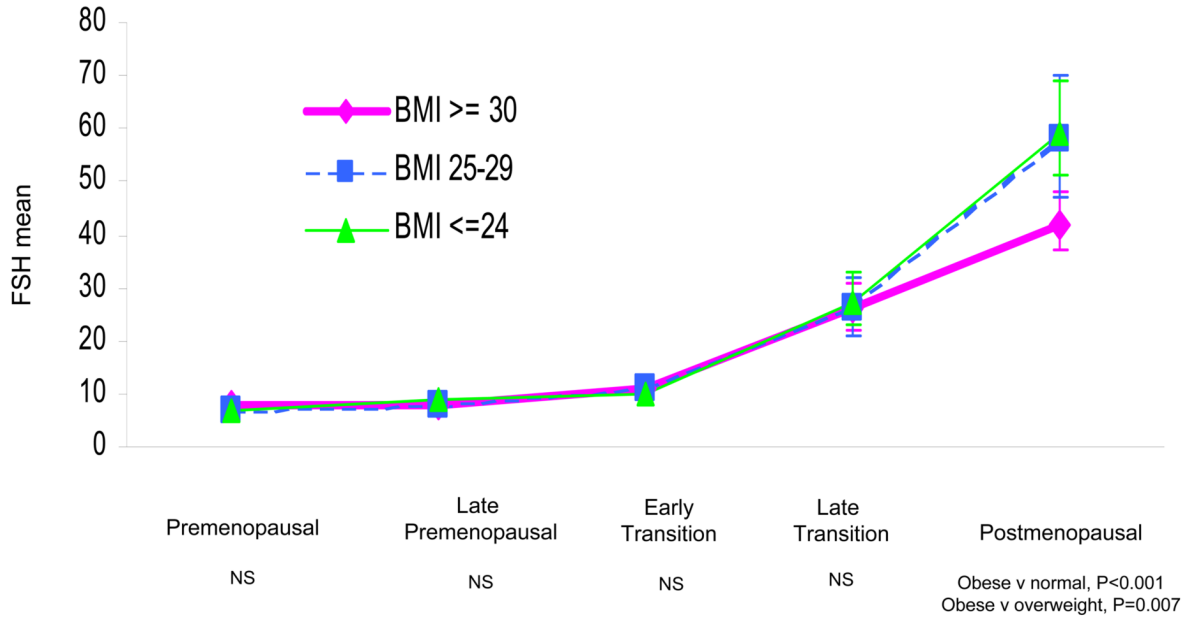
39. Janssen, I.; Powell, LH.; Kazlauskaite, R.; Dugan, SA. Obesity. Silver Spring: 2009 Aug 20. Testosterone and Visceral Fat in Midlife Women: The Study of Women's Health Across the Nation (SWAN) Fat Patterning Study. [Epub ahead of print]

Figure 1 A



BMI X menopausal stage: P<0.001

Figure 1 B



BMI by menopausal stage: P=0.008

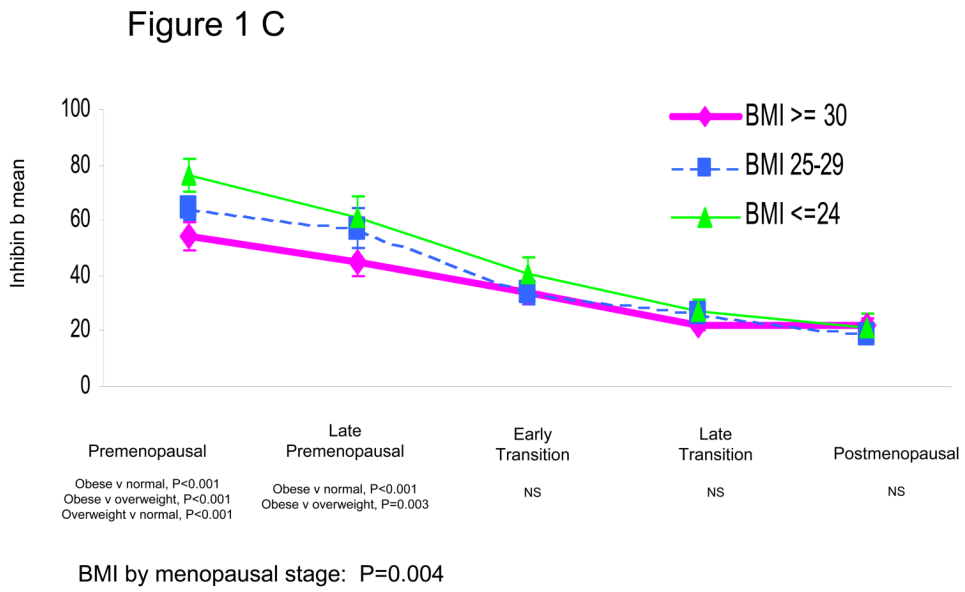


Figure 1.

Interaction between body mass index (BMI) and menopausal stage for (A) estradiol (P<0.001), (B) FSH (P=0.008), and (C) inhibin b (P=0.004) from the full multivariable models. Hormone values are the geometric mean with 95% confidence interval, estimated from multivariable models that adjusted for race, age and smoking and within women correlation due to repeated measurements. The reduced significance level with the Bonferroni correction for within-group comparisons at each menopausal stage is P=0.003.

N=436 with 3,581 observations for estradiol, 3,578 observations for FSH and 3,051 observations for inhibin b.

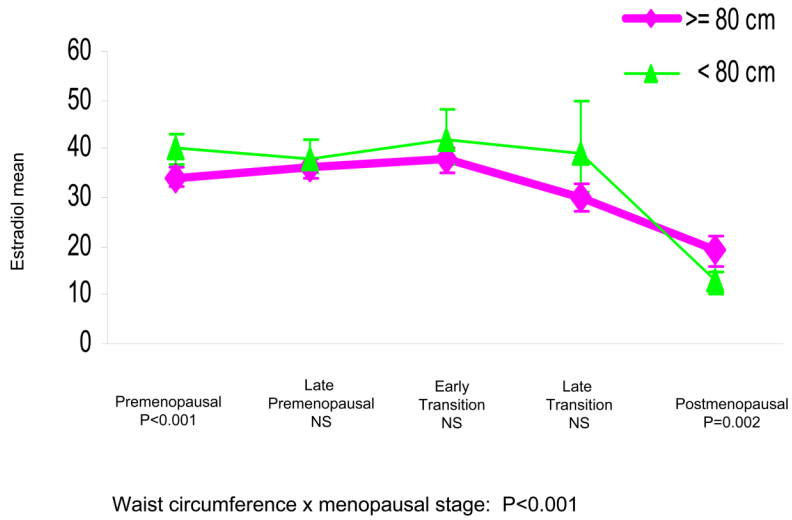


Figure 2.

Interaction between waist circumference (WC) and menopausal stage for estradiol (P<0.001) from the full multivariable model. See legend details in Figure 1.

TABLE 1

Participant characteristics at baseline

Variable	Continued (n = 299)	Discontinued (n = 137)	*P*
Age at V1, y	41.4 (± 3.5)	41.4 (±3.4)	0.857
BMI, kg/m^2	29.3 (±8.4)	29.2 (±6.8)	0.959
Waist circumference, cm			0.222
<80	112 (38)	43 (32)	
≥80	179 (62)	90 (68)	
Waist-to-hip ratio			0.172
<0.80	133 (46)	72 (54)	
0.80 to <0.85	87 (30)	29 (22)	
≥0.85	70 (24)	32 (24)	
Current smoker	109 (37)	56 (41)	0.420
Race			0.091
African American	141 (47)	77 (56)	
White	159 (53)	59 (43)	
No. of children			0.592
0	50 (17)	18 (13)	
1–3	211 (71)	101 (74)	
≥4	35 (12)	18 (13)	
Age at menarche, y	12.6 (±1.7)	12.8 (±1.9)	0.480
Estradiol, pg/mL	41.1 (28.8)	50.0 (±55.5)	0.471
FSH, mIU/mL	7.8 (±4.5)	8.6 (±6.1)	0.204
Inhibin B, ng/mL	74.7 (47.3)	78.7 (±47.3)	0.436

Data are mean (±SD) or n (%). Variable n's vary slightly due to missing data. Menopausal stage not shown because all participants were premenopausal at baseline. BMI, body mass index; FSH, follicle-stimulating hormone.

TABLE 2

Mean unadjusted associations of each study variable with mean hormone levels

Variable	Estradiol, pg/mL		FSH, mIU/mL		Inhibin B, ng/mL	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
BMI, kg/m^2						
≤24[a]	37.7	35.2–40.4	9.03	8.24–9.90	59.1	54.4–64.2
25–29	33.6	31.4–35.9[b]	10.9	10.0–11.9[c]	48.7	45.1–52.5[c]
≥30	30.3	28.5–32.1[c]	13.2	12.1–14.4[c]	39.8	36.7–43.0[c]
Waist circumference, cm						
<80	37.3	34.5–40.3[c]	8.88	8.12–9.71[c]	58.4	53.9–63.3[c]
≥80	32.3	30.8–33.8	11.9	11.2–12.7	44.7	42.2–47.4
Waist-to-hip ratio						
<80[a]	36.1	34.2–38.2	9.24	8.63–9.89	54.6	51.1–58.4
0.80–0.84	33.7	31.9–35.7[d]	13.1	12.2–14.1[c]	46.8	43.6–50.2[c]
≥85	31.2	29.5–32.9[c]	10.8	10.0–11.6[c]	42.9	40.0–46.0[c]
Menopausal stage						
Premenopausal[a]	35.8	34.2–37.6	7.28	7.03–7.54	64.8	61.3–68.4
Late premenopausal	36.5	34.5–38.6	8.33	7.95–8.73[c]	53.5	49.6–57.6[c]
Early transition	37.9	35.6–40.3	10.8	10.2–11.4[c]	36.2	33.9–38.6[c]
Late transition	30.7	28.1–33.5[c]	26.4	23.6–29.4[c]	24.1	22.4–25.8[c]
Postmenopausal	16.7	14.7–19.0[c]	50.5	45.8–55.7[c]	20.5	18.5–22.7[c]
Smoking						
Yes	35.6	33.4–38.0[d]	10.1	9.2–11.0[c]	51.7	47.4–56.4[d]
No	32.4	30.8–34.1	11.6	10.9–12.5	46.2	43.3–49.3
Race						
African American	32.2	30.3–34.2	10.9	10.1–11.7	46.7	43.3–50.5
White	34.8	32.8–36.8	11.3	10.5–12.2	49.5	45.8–53.4

Variable	Estradiol, pg/mL		FSH, mIU/mL		Inhibin B, ng/mL	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Age at V1	0.96	0.95–0.97[c]	1.08	1.07–1.10[c]	0.93	0.92–0.94[c]
Age at menarche	1.01	0.99–1.04	0.98	0.95–1.01	1.03	1.00–1.06
No. of children						
0	33.4	30.6–36.5	11.3	10.0–12.8	45.5	39.5–52.4
1–3[a]	33.8	32.1–35.5	10.8	10.1–11.5	49.4	46.3–52.7
≥4	32.0	28.1–36.4	12.8	10.8–15.1	44.4	38.2–51.6

Hormone values are the geometric means (the natural log back-transformed) in association with class variables and the exponentiated estimate in association with continuous variables over the study interval. N = 436 with 3,670 observations for estradiol, 3,367 observations for FSH, and 3,078 observations for inhibin B. BMI, body mass index; FSH, follicle-stimulating hormone.

[a] The reference group in general linear regression analysis.

[b] $P < 0.01$.

[c] $P < 0.001$.

[d] $P < 0.05$.