

Hormones and Sexuality During Transition to Menopause

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OBJECTIVE: To examine the relationship between reproductive hormonal dynamics and sexual dysfunction assessed in a cohort of women approaching menopause.

METHODS: Women in the Penn Ovarian Aging Study were assessed at yearly intervals for 3 years with early follicular hormone measurements (estradiol, follicle-stimulating hormone, luteinizing hormone [LH], sex hormone binding globulin, dehydroepiandrosterone sulfate [DHEAS], total testosterone), anthropometric measures, and extensive questionnaires including the Female Sexual Function Index. Univariable analyses were performed to determine the association between hormones, menopausal status, and sexual dysfunction. Multivariable linear and logistic regression models were created to examine the influence of hormones on sexual function adjusting for the effect of potential confounders.

RESULTS: The final multivariable model indicated that sexual dysfunction increased with advanced menopausal status, with postmenopausal women being 2.3 times as likely to experience sexual dysfunction compared with premenopausal women (odds ratio 2.3, 95% confidence interval [CI] 1.3–4.1). Low DHEAS serum concentrations were associated with decreased sexual function (odds ratio 1.59, 95% CI 1.19–2.14). Additional risk factors

associated with sexual dysfunction included absence of a sexual partner (11.2, 95% CI 6.9–18.1), high anxiety (3.8, 95% CI 1.6–9.2), and children under the age of 18 living at home (1.6, 95% CI 1.1–5.5). Lubrication, orgasm, and pain were specific aspects of sexuality negatively affected by menopause.

CONCLUSION: This study confirms the observation that sexual dysfunction increases over the menopausal transition. Several factors associated with sexual dysfunction include low DHEAS, absence of a sexual partner, anxiety, and children under the age of 18 living at home.

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LEVEL OF EVIDENCE: II

Sexual dysfunction is broadly defined by DSM-IV as “A disturbance in the processes that characterize the sexual response cycle or by pain associated with sexual intercourse.”¹ Female sexual dysfunction is extremely prevalent in the United States, affecting more than 40% of women aged 18–59 years. While sexual dysfunction appears to be more prevalent in women than in men, minimal research has been dedicated to the sexual problems of women.² In part, this lack of attention may be due to the complexity of female sexuality; indeed, female sexuality appears to be influenced by a variety of emotional, psychological, and physiologic factors.^{2–12}

There is evidence that sexual dysfunction increases through the menopausal transition.^{3,4} In a cross-sectional study of women aged 45–55 years, Dennerstein et al³ found that 31% reported a decrease in sexual interest, particularly sexual responsiveness from premenopause to late perimenopause period. In addition, other aspects of sexual functioning such as frequency of sexual intercourse, libido, vaginal dyspareunia, and partner problems were also exacerbated during the late perimenopause to postmenopausal time period.

Physiologically, it is currently unclear why sexual function declines during the natural transition

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through menopause. Specifically, the relationship between hormonal changes and sexuality during this period remains elusive.^{11,13–16} Coincident with decreasing sexual interest, circulating androgens decline during the late reproductive years with androgen levels at age 45 approximately one-half that of women in their 20s.^{17,18} There is mounting evidence that fluctuations in hormone measures over time, rather than absolute levels, are associated with increased symptoms of other conditions such as premenstrual dysphoric disorder.^{19,20} We have shown that variability in total testosterone levels over a 4-year period in 326 women during the late reproductive years was associated with decreased libido.¹²

The objective of this study was to examine the relationship between reproductive hormonal dynamics and sexual dysfunction and also identify other risk factors for sexual dysfunction, in a cohort of women approaching menopause. The primary hypothesis was that sexual function scores would be lower among women whose free testosterone fluctuation was in the upper 25% compared with women with fluctuation in the lowest 25%. To test this hypothesis, levels of reproductive hormones including free testosterone, and sexual function, assessed by a validated sexual function instrument (Female Sexual Function Index), were measured over a 3-year period.

MATERIALS AND METHODS

The Penn Ovarian Aging Study is a longitudinal study of a randomly identified population-based cohort, which was designed to enroll equal numbers of African-American (n=218) and white (n=218) women. The main aim of the project was to examine associations between variability and changes in reproductive hormones and symptoms associated with ovarian aging. The cohort was recruited from 1996 to 1997 in Philadelphia County by random-digit dialing as described elsewhere.^{21,22} Eligibility criteria were age 35–47 years at enrollment, menstrual cycles in normal range (22–35 days) for the previous 3 months, an intact uterus, and at least one ovary. Exclusion criteria included current use of hormonal or psychotropic medications including hormonal contraception and hormone replacement therapies, hysterectomy, currently pregnant or breastfeeding, serious health problems known to compromise ovarian function (eg, diabetes, liver disease, breast or endometrial cancer) and alcohol or drug abuse within the past year. The study was approved by the University of Pennsylvania Institutional Review Board, and written, informed consent was obtained from all participants.

Over the past 9 years, there has been a total of 10 study assessment periods initially spaced 8 months apart, and more recently at yearly intervals. Data for this investigation were obtained during a 3-year period at study assessments 8, 9, and 10. At each assessment period, participants were assessed during the first 6 days of the menstrual cycle with hormone measurements, anthropometric measures, and extensive questionnaires including the Female Sexual Function Index.²³ Specific information on menstrual cycle dates, reproductive history, general health status and behaviors, sexual function, and demographics was obtained. Each yearly assessment period had two visits, scheduled between days 1 and 6 of two consecutive menstrual cycles, to obtain blood samples for the hormone assays. Assessment periods occurred at any time in nonmenstruating women. All data collection was obtained by trained research interviewers in individual interviews at the participants' homes.

Blood samples, on average, were obtained on cycle day 4. They were centrifuged and frozen in aliquots at -80°C . Total testosterone, dihydroepiandrosterone sulfate (DHEAS), estradiol (E2), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured at each visit by radioimmunoassay using Coat-A-Count commercial kits (Diagnostic Products, Los Angeles, CA). Assays were conducted in batched samples of 20 women, including 4 samples per woman from four different time points. Interassay and intraassay coefficients of variation were consistently less than 5% for all hormones measured. Sex hormone binding globulin was measured by immune-radiometric assay using a Diagnostic Systems Laboratory kit (Webster, TX). The interassay and intraassay coefficients of variation were between 2.5% and 6.0%. Free testosterone was calculated using the values for sex hormone binding globulin and total testosterone using the modified Sodergard equation.²⁴

All laboratory assessments were completed in the laboratory of the Clinical Research Center of the Hospital of the University of Pennsylvania. Assays were batched and run for this population only. They were performed in duplicate for all hormones and repeated if values differ by more than 15%.

The Female Sexual Function Index is a 19-item, multi-dimensional, self-report instrument for assessing the key dimensions of sexual function in women. Domains include desire, arousal, lubrication, orgasm, satisfaction, and pain. The maximum score for each domain is 6, and the maximum total score is 36. Of all instruments demonstrating acceptable reliability, the Female Sexual Function Index is the only published



instrument validated and scaled on a sample of women with clinically diagnosed female sexual dysfunction. Specifically, the questionnaire has been found to be valid and reliable in women with sexual arousal disorder, orgasmic disorder, and hypoactive sexual desire disorder. Mean total scores for women with sexual dysfunction were 19.2 and 19.7 compared with 30.5 in women with normal sexual function.^{23,25} In the present study, the Female Sexual Function Index score was examined as both a continuous and a dichotomous outcome using a score of less than 20 to define sexual dysfunction. Even though cutoff values of 26 have been recently published for this instrument, a cutoff of 20 was felt to provide a more rigorous and conservative estimate of sexual dysfunction in this population.²⁶

The length of the current menstrual cycle was determined from the menstrual date at the study interview (interviews were conducted within 6 days of bleeding) and the two previous menstrual dates recorded in the structured interview. Confirmatory dates were obtained from the menstrual diaries recorded by the participants for one menstrual cycle at each assessment. The definitions of menopausal stage were adapted from the consensus statement on a staging system for reproductive aging in women.^{27,28} At each assessment, the participant was assigned to one of the following categories based on menstrual bleeding patterns at that assessment: premenopausal, regular menstrual cycles in the 22–35 day range; early transition, change in cycle length 7 or more days in either direction in at least one or two menstrual cycles compared with the participant's personal baseline at enrollment in the cohort; late transition, 3–11 months of amenorrhea during the study; and postmenopausal, 12 or more months of amenorrhea with no hysterectomy.

At each assessment period, body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (meters) using the average of duplicate measures of height and weight at each assessment. The categorical grouping of BMI (less than 25, 25–30, 30 or higher) was used in the final regression model because of its appropriateness for the distribution of the data and its clinical relevance. Anxiety was assessed using the Zung Anxiety Index, a validated, 20-item self-report measure that is sensitive to the frequency of affective and somatic anxiety symptoms. The frequency of each item was rated from none (1) to most or all the time (4), and ratings were summed for a total score. Zung established score ranges to classify normal anxiety (20–35), mild to moderate anxiety (36–47), and high anxiety (48–60).²⁹

Depression was assessed using the Center for Epidemiologic Studies Depression Scale, a 20-item self-report inventory for assessing current depressive symptoms. The standard Center for Epidemiologic Studies Depression Scale cutoff score of 16 or greater was used to define high depressive symptoms.³⁰ Any smoking and alcohol intake over the prior 12 months was categorized as a positive response. The number of children aged less than 18 years at home was assessed at each assessment period, and a positive response was defined as a response of 1 or greater. Absence of a partner was defined as no partner over the past 12 months. Sexual abuse was defined as a positive response to the question: "Has a stranger or anybody you know every made you have sex against your will?"

A priori estimates of statistical power were conducted to assess the detectable difference in overall Female Sexual Function Index scores which would be measurable given the Penn Ovarian Aging Study sample. We estimated that we would be able to detect a difference in Female Sexual Function Index scores of 2.9 points given several assumptions based on previously conducted research: (1) normal distribution of Female Sexual Function Index scores with a standard deviation (SD) =6.63, (2) power of 80%, (3) alpha of 0.05, and (4) sample size of 353. However, in the implementation of this study, several of these assumptions were incorrect. In particular, the sample size was reduced to 311 due to loss to follow-up, the standard deviation in Female Sexual Function Index was quite large (SD=11), and the distribution of outcomes within our sample appeared to be bimodal, facilitating the need for a binary response variable and reducing statistical power to assess associations between sexual dysfunction and hormones. There was adequate power to detect a 0.5 SD difference in means between women with sexual dysfunction compared with those with normal sexual function.

The distribution of data for the study sample was inspected using histograms and Q-Q plots. Because the overall sexual function score appeared bimodal in distribution, the overall sexual function score from the Female Sexual Function Index was dichotomized for the purposes of statistical analysis, with a score less than 20 defining sexual dysfunction. Scores of the domains of desire, arousal, lubrication, orgasm, and satisfaction were normally distributed and therefore mean scores were analyzed. However, because pain domain scores appeared bimodal in distribution, a score of 3 or less was used to define sexual pain. All hormone measures were transformed to log values to accommodate assumptions of the statistical models.



We examined both mean hormone values and fluctuation in hormone values with sexual dysfunction over time. Hormone fluctuation was measured as the individual-specific standard deviation of hormones over time around the woman's average level.

Univariable analyses were conducted to assess the association between reproductive hormones and other variables of interest and overall sexual dysfunction. Logistic regression models for repeated measures were used to estimate the independent effects on sexual dysfunction of each of the covariates individually (univariable models) and then adjusted for all other variables in the model (multivariable models). Variance estimates for the Wald statistics of the true logistic parameters were adjusted for the repeated observations from each participant using Generalized Estimating Equations.³¹ Important variables of interest explored in univariable analyses included menopausal status, cycle day of blood draw, body mass index, age, race, education, number of children under the age of 18 living at home, anxiety (Zung), depression (Center for Epidemiologic Studies Depression Scale), presence of a partner, use of hormone therapy, use of psychiatric medications, and a history of sexual abuse. Individual observations were censored if a participant was using hormonal medication, pregnant, or lactating or had a hysterectomy or bilateral salpingo-oophorectomy.

To adjust for the influence of other covariates on sexual dysfunction, we created separate hormone-specific multivariable logistic regression models using a backward elimination strategy to examine the influence of hormones on sexual function adjusting for the effect of potential confounders. A variable was considered a confounder and included in the model if the estimate changed by 15% or if the variable was associated with the outcome (Female Sexual Function Index score) with a $P \leq .2$.³² Given the importance of partner status, an analysis stratified on partner status was performed. All analyses were conducted using SAS v9.1 (SAS Institute Inc, Cary, NC). A two-sided P value of <0.05 was considered significant.

Finally, factors associated with specific domains of sexual functioning (desire, arousal, lubrication, satisfaction, orgasm, pain) were considered. Univariable analyses were performed assessing the association between each hormone summary (ie, mean and variability), other variables of interest, and the domains of sexual function. Linear regression models for repeated measures were performed to assess the association between variables associated with the domains of sexual dysfunction and known confounders which took into account the repeated measure-

ments contributed by each participant, as was done above for the logistic models. To adjust for multiple comparisons in the domain analysis, a P value of $<.008$ was considered statistically significant.

RESULTS

Of the 436 women originally enrolled in the Penn Ovarian Aging Study, 313 participated at assessment period 8 and 311 patients at assessment 10. Only 2 patients were lost to follow-up over 3 years. Table 1 compares demographic characteristics of the cohort at assessments 8 and assessment 10. The proportion of premenopausal women decreased from 46% to 31%. At assessment 10, 27% were in the early transition, 17% in the late transition, and 19% had reached menopause. Follicle-stimulating hormone and LH increased over the 3 year period, while DHEAS decreased slightly. A comparison of the baseline values for all variables in this study between active and inactive participants compared with baseline at assessment 1 showed no differences in racial, demographic, or hormone parameters.³³

Of the 311 women participating in this study at assessment 10, 102 (33%) were categorized as having sexual dysfunction with an Female Sexual Function Index score 20 or below, while 209 (67%) had score higher than 20. Overall, the mean Female Sexual Function Index score was 22.9 (SD 11.0). Mean domain scores were desire 3.37 (SD 1.25), arousal 3.37 (SD 2.18), lubrication 3.73 (SD 2.47), orgasm 3.55 (SD 2.42), satisfaction 3.92 (SD 1.77), and pain 3.90 (SD 2.64).

Univariable associations between risk factors and dichotomous sexual dysfunction outcome (Female Sexual Function Index score 20 or below) are presented in Table 2. Cross-sectional hormone analyses revealed that DHEAS levels were significantly lower in women experiencing sexual dysfunction compared with those without dysfunction at assessment 10 (geometric mean DHEAS 66.52 ng/dL, 95% confidence interval [CI] 58.22–75.99 versus 81.08 ng/dL 95% CI 74.58–88.14). Other variables associated with sexual dysfunction in unadjusted analyses included advanced menopausal stage, obesity, African-American race, presence of children aged less than 18 years living at home, anxiety, depression, lack of a sexual partner, alcohol use, and history of sexual abuse. No significant associations were noted between sexual function and other reproductive hormone levels or variability, including free testosterone, age, education, smoking, cycle day of blood draw (not shown), and use of hormonal or psychotropic medications (not shown).



Table 1. Study Variables at Assessment 8 and Assessment 10

| | Assessment 8 (N=313) | Assessment 10 (N=311) |
|--|-----------------------------|-----------------------------|
| Age (y) | | |
| 40–44 | 112 (36) | 56 (18) |
| 45–49 | 131 (42) | 139 (45) |
| 50–54 | 70 (22) | 111 (35) |
| 55–59 | 0 | 5 (2) |
| Race | | |
| Caucasian | 162 (52) | 160 (51) |
| African American | 151 (48) | 151 (49) |
| Menopausal status | | |
| Premenopausal | 144 (46) | 96 (31) |
| Early transition | 95 (30) | 85 (27) |
| Late transition | 40 (13) | 53 (17) |
| Postmenopausal | 22 (7) | 58 (19) |
| Pregnant/Lactating | 0 | 1 (<1) |
| Hysterectomy or BSO | 12 (4) | 18 (6) |
| BMI | | |
| Lower than 25 | 100 (33) | 87 (28) |
| 25–30 | 75 (24) | 79 (25) |
| Higher than 30 | 132 (43) | 136 (44) |
| Anxiety | | |
| None | 220 (70) | 233 (75) |
| Mild to moderate | 78 (25) | 71 (23) |
| High | 15 (5) | 7 (2) |
| Depression | 110 (35) | 86 (28) |
| Mean Female Sexual Function Index score (SD) | 22.9 (+10.95) | 21.8 (+11.19) |
| Mean total testosterone (ng/dL, SD) [range] | 16.3 (+11.16) [0.74–61.66] | 17.6 (+11.30) [0.58–82.28] |
| Mean free testosterone (pg/mL, SD) [range] | 0.2 (+0.17) [0.01–1.04] | 0.2 (+0.18) [0.01–1.46] |
| Mean DHEAS (ug/dL, SD) [range] | 95.0 (+54.83) [2.19–445.15] | 91.4 (+54.00) [4.65–347.15] |
| Mean estradiol (pg/mL, SD) [range] | 53.7 (+43.96) [4.25–296.05] | 45.2 (+41.49) [0.79–320] |
| Mean FSH (mIU/mL, SD) [range] | 18.1 (+19.18) [1.52–92.97] | 33.5 (+28.37) [1.98–123.05] |
| Mean LH (mIU/mL, SD) [range] | 10.1 (+13.15) [0.68–73.11] | 14.9 (+18.37) [0.49–190.70] |

BSO, bilateral salpingo-oophorectomy; BMI, body mass index; SD, standard deviation, DHEAS, dihydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Anxiety was assessed using the Zung questionnaire: normal anxiety (score 20–35), mild to moderate anxiety (score 36–47), and high anxiety (score 48–60). Depression was assessed using the Center for Epidemiologic Studies Depression Scale (score 16 or higher consistent with depression). The Female Sexual Function Index has a maximum score of 36; sexual dysfunction has been defined as a score of less than 20.

Results of the final multivariable logistic regression model are also presented in Table 2. After adjusting for race, BMI, children aged less than 18 years living at home, DHEAS levels, anxiety, and partner status, the final multivariable model revealed that *higher* mean DHEAS levels were protective of sexual dysfunction (OR 0.63, 95% CI 0.47–0.84) (while *lower* DHEAS levels were associated with sexual dysfunction). In addition, sexual dysfunction increased with advanced menopausal status, with women in the late transition being 2.4 times and postmenopausal women being 2.3 times as likely to experience sexual dysfunction compared with premenopausal women. Other factors associated with sexual dysfunction included absence of a sexual partner (11.2, 95% CI 6.9–18.1), high anxiety (3.8, 95% CI 1.6–9.2), and children aged less than 18 years living at home (1.6, 95% CI 1.1–5.5). A history of

sexual abuse and alcohol use was not statistically significant after adjusting for other variables and were therefore dropped from the multivariable model. Further analysis revealed that anxiety and depression were significantly correlated. Because anxiety was more strongly related to sexual dysfunction after controlling for other important variables, anxiety was included in the multivariable model rather than depression.

Due to the importance of sexual partner in the analyses and the fact that a substantial proportion of women did not have a sexual partner ($n=81$), an analysis was performed restricting the sample to only those women with a sexual partner. The associations did not change substantially when the analysis was restricted to women with a partner. While restricting our sample would not have changed our findings, the power to detect differences in sexual function by



Table 2. Unadjusted and Adjusted Associations of Sexual Dysfunction and Selected Variables

| | Unadjusted OR (95% CI) | <i>P</i> | Adjusted OR (95% CI) | <i>P</i> |
|---------------------------------|---------------------------|-----------|-------------------------|-----------|
| Age (y) | | .13 | | |
| 40–44 | Reference | Reference | | |
| 45–49 | 1.43 (0.93–2.21) | .10 | | |
| 50–54 | 1.65 (1.01–2.69) | .04 | | |
| Race | | | | |
| Caucasian | Reference | Reference | Reference | Reference |
| African American | 1.46 (0.98–2.18) | .07 | 0.92 (0.58–1.47) | .73 |
| Menopausal status | | .035 | | .004 |
| Premenopausal | Reference | Reference | Reference | Reference |
| Early transition | 1.39 (1.00–1.93) | .05 | 1.37 (0.88–2.14) | .16 |
| Late transition | 1.84 (1.23–2.74) | .003 | 2.43 (1.42–4.14) | .001 |
| Postmenopausal | 1.89 (1.16–3.10) | .01 | 2.31 (1.30–4.12) | .004 |
| BMI | | .008 | | .067 |
| Lower than 25 | Reference | Reference | Reference | Reference |
| 25–30 | 1.91 (1.26–2.90) | .003 | 1.32 (0.76–2.27) | .32 |
| Higher than 30 | 1.71 (1.10–2.69) | .02 | 1.82 (1.10–3.03) | .02 |
| Children at home | 1.24 (0.88–1.76) | .022 | 1.63 (1.07–5.51) | .02 |
| Anxiety | | .02 | | .01 |
| None | Reference | Reference | Reference | Reference |
| Mild to moderate | 1.35 (0.97–1.88) | .08 | 1.32 (0.85–2.05) | .21 |
| High | 2.35 (1.25–4.42) | .008 | 3.80 (1.57–9.22) | .003 |
| Depression | 2.04 (1.45–2.85) | <.001 | | |
| Less than high school education | 1.34 (0.89–2.0) | .157 | | |
| Sexual abuse | 1.64 (1.02–2.62) | .04 | | |
| Alcohol | 0.39 (0.22–0.69) | .001 | | |
| Smoking | 1.30 (0.89–1.90) | .18 | | |
| Absence of partner | 11.1 (7.10–17.37) | <.001 | 11.19 (6.93–18.08) | <.001 |
| Mean total testosterone* | 1.02 (0.87–1.21) | .78 | | |
| Mean free testosterone* | 1.03 (0.88–1.20) | .71 | | |
| Mean DHEAS* | 0.72 (0.55–0.94) | .02 | 0.63 (0.47–0.84) | .002 |
| Mean estradiol* | 0.95 (0.82–1.10) | .40 | | |
| Mean FSH* | 1.11 (0.92–1.34) | .26 | | |
| Mean LH* | 1.0 (0.88–1.14) | 1.00 | | |

OR, odds ratio; CI, confidence interval; BMI, body mass index; SD, standard deviation, DHEAS, dihydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Note that adjusted variables are only shown for those that remained in multivariate analysis. Sexual dysfunction defined as overall Female Sexual Function Index score less than 20. Anxiety was assessed using the Zung questionnaire: normal anxiety (score 20–35), mild to moderate anxiety (score 36–47), and high anxiety (score 48–60). Depression was assessed using the Center for Epidemiologic Studies Depression Scale (score 16 or higher consistent with depression). Alcohol and smoking were defined as any alcohol intake or smoking over the past 12 months. Children at home was defined as any children aged less than 18 years living at home.

* Adjusted for menopausal stage.

menopausal status decreased when all women without a partner were eliminated from the analysis. Therefore to augment the power of the analysis we have left those women without a partner in the analysis.

To further examine the association between DHEAS and sexual dysfunction, DHEAS was examined as a categorical variable (divided in quartiles). Table 3 illustrates the association between DHEAS quartiles and sexual dysfunction. Women with sexual dysfunction were twice as likely to have DHEAS levels in the lowest quartile.

Table 4 presents the results of the multivariable models assessing the association between menopausal

stage and other variables of interest with each domain score. While scores for all of the domains declined over the menopausal transition from premenopause to the late transition stage, only scores for lubrication reached statistical significance adjusting for multiple comparisons (overall *P* values: desire *P*=.14; arousal *P*=.05; lubrication *P*=.002; orgasm *P*=.019; satisfaction *P*=.23). Additionally, the odds of sexual pain increased from premenopause to late transition (OR 2.18, *P*=.02).

Higher DHEAS levels were associated with improved scores of all sexual functioning domains, statistically significant with a *P*<.008 for orgasm, lubrication, and pain. Lack of a sexual partner was



Table 3. Adjusted Associations Between DHEAS Quartiles and Sexual Dysfunction

| DHEAS Quartiles | OR (95% CI) | P |
|-----------------|------------------|-----------|
| Top quartile | 0.60 (0.31–1.16) | .13 |
| 3rd quartile | 0.82 (1.14–3.77) | .55 |
| 2nd quartile | Reference | Reference |
| Lowest quartile | 2.07 (1.14–3.77) | .02 |

DHEAS, dihydroepiandrosterone sulfate; OR, odds ratio; CI, confidence interval.

Overall $P < .001$.

Model adjusted for menopausal status, body mass index, children at home, race, partner status, and anxiety.

significantly negatively associated with all of the sexual function domains. The presence of children aged less than 18 years at home was negatively associated with the domains of arousal, orgasm, and satisfaction. Higher anxiety levels were associated with all sexual functioning domains.

DISCUSSION

The objective of this study was to examine the relationship between reproductive hormonal dynamics and sexual dysfunction and identify other risk factors associated with sexual dysfunction during the menopausal transition. This is one of the few studies published to date that assesses reproductive hormones and sexual function using a validated measure with repeated measures over time. This study confirms the observation that sexual dysfunction increases over the transition through menopause. Higher DHEAS levels were associated with a decreased odds of reporting sexual dysfunction. That is, women with the lowest levels were most likely to report sexual dysfunction. In addition, other factors associated with sexual dysfunction included absence of a sexual partner, anxiety, and children aged less than 18 years living at home. We were unable to detect a significant association between other reproductive hormone levels or fluctuation and sexual dysfunction in this study.

Female sexual dysfunction is extremely prevalent in the United States and increases through the menopausal transition.^{2–4} While estimates of sexual dysfunction during the transition are as high as 88%,¹² the 33% prevalence of sexual dysfunction in the current study is consistent with previous population-based studies estimating that 27–31% of women approaching menopause experience an increase in sexual problems.^{3,4} In particular, we observed an overall increase in sexual dysfunction during the transition, which was particularly dramatic from premenopause

to the late transition, after adjusting for other variables associated with sexual dysfunction. Specifically, women in the late transition were 2.4 times as likely to experience sexual dysfunction compared with premenopausal women.

Particular aspects of sexual dysfunction that worsened over the transition to the late transition stage included desire, arousal, lubrication, and pain. These findings are consistent with previous reports from an Australian longitudinal study which observed a peak in sexual problems during the late transition, particularly affecting libido, sexual frequency, positive feelings for the partner, and dyspareunia.^{3,34} Other studies have reported a significant decline in the frequency of sexual fantasy, foreplay, and intercourse and problems with vaginal lubrication.³⁵

The association between reproductive hormone levels and sexual dysfunction during the menopausal transition has been uncertain. While some studies have implicated a decline in estrogen or androgen levels, findings have been contradictory and inconclusive.^{11,13–15} In the current study, higher mean DHEAS levels appeared to be protective of sexual dysfunction in initial unadjusted analyses and final multivariable model. Notably, we found that women reporting sexual dysfunction were more than twice as likely to have DHEAS levels in the lowest quartile. We did not find that mean total and free testosterone levels, or the variability in reproductive hormone measures, were associated with sexual dysfunction as previously hypothesized.¹²

These hormone findings were consistent across all domains of sexual functioning and are supported by a recently published large cross-sectional study conducted in Australia. Those authors observed that women aged more than 45 years with decreased sexual responsivity scores were almost 4 times as likely to have serum DHEAS levels below the 10th percentile compared with women with normal responsivity scores. Similar to our study, other androgens such as testosterone were not associated with sexual function in that report.³⁶

It must be emphasized that circulating reproductive hormone values that are assayed in this and other such studies may not be reflective of actual tissue exposure or action. Dihydroepiandrosterone sulfate is a major precursor for androgens and estrogens within the body, and it is not possible to determine if DHEAS itself or one of its metabolites is responsible for the observed association with sexual functioning.³⁷ As such, at this point measurement of androgen values are generally not helpful in the clinical setting



Table 4. Mean Female Sexual Function Index Domain Scores (and Odds of Pain) for Each Variable

| | Desire Score | Arousal Score | Lubrication Score | Orgasm Score | Satisfaction Score | Pain OR (95% CI) |
|---------------------|--------------|---------------|-------------------|--------------|--------------------|---------------------|
| Race | | | | | | |
| African American | 3.35 (0.13) | 2.76 (0.18) | 2.86 (0.21) | 2.83 (0.20) | 3.26 (0.16) | 0.72 (0.46–1.14) |
| Caucasian | 2.91 (0.13)* | 2.68 (0.20) | 2.86 (0.22) | 2.77 (0.22) | 3.12 (0.15) | Reference |
| Menopausal status | | | | | | |
| Premenopause | 3.26 (0.12) | 2.99 (0.18) | 3.24 (0.22) | 3.17 (0.21) | 3.37 (0.14) | Reference |
| Early transition | 3.19 (0.13) | 2.90 (0.19) | 3.16 (0.22)† | 2.99 (0.21)† | 3.23 (0.15) | 1.03 (0.66–1.61) |
| Late transition | 2.94 (0.16) | 2.52 (0.23)‡ | 2.54 (0.26)† | 2.55 (0.25)† | 3.10 (0.18) | 2.18 (1.27–3.75)† |
| Postmenopausal | 3.12 (0.15) | 2.48 (0.22) | 2.49 (0.25) | 2.50 (0.25) | 3.04 (0.21) | 1.44 (0.80–2.59) |
| BMI | | | | | | |
| Lower than 25 | 3.23 (0.13) | 2.94 (0.20) | 3.07 (0.24) | 3.10 (0.23)‡ | 3.30 (0.17) | Reference |
| 25–30 | 3.19 (0.14) | 2.60 (0.20) | 2.73 (0.22) | 2.63 (0.21)‡ | 3.06 (0.17) | 1.55 (0.90–2.65) |
| Higher than 30 | 2.97 (0.13)‡ | 2.62 (0.19) | 2.78 (0.22) | 2.67 (0.21) | 3.19 (0.15) | 1.13 (0.67–1.91) |
| Children at home | 2.94 (0.13) | 2.54 (0.19)‡ | 2.75 (0.21) | 2.58 (0.20)† | 2.99 (0.15)‡ | 1.15 (0.76–1.76) |
| No children at home | 3.31 (0.12) | 2.90 (0.18) | 2.97 (0.21) | 3.02 (0.20) | 3.38 (0.15) | Reference |
| Absence of partner | 2.89 (0.16)* | 1.70 (0.23)* | 1.59 (0.27)* | 1.60 (0.26)* | 2.24 (0.18)* | 10.50 (6.76–16.29)* |
| Partner | 3.37 (0.12) | 3.74 (0.16) | 4.13 (0.18) | 4.0 (0.17) | 4.13 (0.13) | Reference |
| Anxiety | | | | | | |
| None | 3.36 (0.08) | 1.08 (0.12) | 3.28 (0.13) | 3.23 (0.13) | 3.58 (0.09) | Reference |
| Mild to moderate | 3.20 (0.11) | 2.76 (0.15)‡ | 2.99 (0.18) | 2.88 (0.18)‡ | 3.28 (0.14)‡ | 1.0 (0.60–1.54) |
| High | 2.82 (0.27)‡ | 2.32 (0.40) | 2.30 (0.46)‡ | 2.29 (0.43)‡ | 2.69 (0.14)† | 3.98 (1.55–10.22) |
| DHEAS mean | 0.17 (0.07)‡ | 0.32 (0.11)‡ | 0.44 (0.12)* | 0.24 (0.13) | 0.26 (0.10)† | 0.64 (0.48–0.86) |

OR, odds ratio; CI, confidence interval; BMI, body mass index; DHEAS, dihydroepiandrosterone sulfate.

Data are presented as mean (standard error). Beta estimate is shown for the DHEAS mean level.

Female Sexual Function Index Domain scores range from 1.2 to 6.0 for desire and 0 to 6 for arousal, lubrication, orgasm, satisfaction, pain.

Anxiety was assessed using the Zung questionnaire: normal anxiety (score 20–35), mild to moderate anxiety (score 36–47), and high anxiety (score 48–60). Depression was assessed using the Center for Epidemiologic Studies Depression Scale (score 16 or higher consistent with depression). Alcohol and smoking were defined as any alcohol intake or smoking over the past 12 months. Children at home was defined as any children aged less than 18 years living at home. Pain is analyzed as a dichotomous variable due to its bimodal distribution, while other domains are normally distributed and analyzed as continuous variables. To adjust for multiple comparisons in the domain analysis, a *P* value of <.008 was considered statistically significant.

* *P* ≤ .05.

† *P* ≤ .01.

‡ *P* ≤ .001.

to assist in the diagnosis and treatment of sexual dysfunction.

This study, as well as the previously cited study, raises the question as to whether DHEAS replacement in women experiencing sexual dysfunction would improve symptoms. At this time, there are no data addressing this question. Nonetheless, DHEAS is being used for a variety of common complaints as an herbal supplement. A randomized controlled trial assessing the safety and efficacy of DHEAS is needed to support its use for the treatment of sexual dysfunction.

Apart from the association between sexual dysfunction and menopausal status and DHEAS, we have observed a significant relationship between sexual dysfunction and anxiety, lack of a sexual partner, and children aged less than 18 years living at home. These findings are consistent with other epidemiologic studies highlighting important factors affecting women's sexuality during the menopausal transition such as relationship issues, mental health, and socio-cultural influences.^{2–12} Not surprisingly, by far the

most important predictor of sexual dysfunction was absence of a partner. While this is not a novel finding and was not of primary interest in this investigation, partner status was adjusted for in the model since restricting the analysis to women with a partner would have diminished the power of the study substantially. Importantly, partner status did not appear to confound the associations of other variables in the model.

Despite our rigorous approach, there are several potential limitations to this study. Although our outcome was measured using a validated instrument, in our population the distribution of this measure had a much larger standard deviation (nearly 2 times greater) than the validation data and appeared bimodal in distribution. Therefore, the power to detect differences for this study was lower than anticipated. In other words, there may be a real association between other reproductive hormones and sexual dysfunction, but we were unable to detect it in this study. The findings from this study will be valuable to plan future adequately powered studies to assess this question.



While testosterone levels are known to fluctuate during the menstrual cycle and there is diurnal variation, all samples were taken during the early follicular phase of the menstrual cycle (days 1–6) in menstruating women to minimize variability in hormones. For logistical reasons, it was not possible to have blood drawn on all women at the same time during the day. While it is possible that this could have resulted in information bias, we believe that this bias was random and would be non-differential with respect to the outcome of interest (sexual dysfunction).³⁸ Therefore, this would have biased our results to finding no association between testosterone and sexual dysfunction. This may contribute to why we did not find a significant association between mean testosterone levels and sexual dysfunction.

While loss to follow up from the original cohort 10 years ago may affect the generalizability of our findings, we found no differences in baseline characteristics between women who stayed in the study compared with those that dropped out.³⁰ Moreover, selection bias in this study should be minimal because only two women were lost over the 3 years during which data were collected for this study. In addition, the associations presented in this manuscript compare premenopausal women with women who are at other stages of menopausal transition. As such, these analyses do not convey the impact of menopausal change within a specific woman over time. However, continued follow-up of these women will enable us to evaluate this research question as well. Finally, selection of variables for the multivariable analysis of the domains of sexual functioning was based on the overall sexual function analysis and consistently applied to each domain. While this was a conservative approach to minimize type I error, it is possible that we did not identify other important variables that might affect individual domain results. Future work will involve further analysis of the individual domains of sexual functioning.

Sexuality is an important aspect of health which affects the overall well-being of all men and women. We found that low DHEAS levels and other factors were associated with decreased sexual functioning in women during the menopausal transition. This study highlights the need to conduct further longitudinal studies to better understand the physiologic basis for sexual dysfunction to develop effective treatments.

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