

# Hormones, mood, sexuality, and the menopausal transition

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**Objective:** To determine the extent of changes in women's sexual functioning and well-being during the menopausal transition and the relationship to hormonal changes.

**Design:** Prospective observational study.

**Setting:** Population-based sample assessed at home.

**Patient(s):** 438 Australian-born women 45–55 of years who were still menstruating at baseline. Of these, 226 were studied for effects of hormones on sexual functioning.

**Main Outcome Measure(s):** Short Personal Experiences Questionnaire (SPEQ) and Affectometer 2 scores and annual blood sampling.

**Result(s):** From the early to late menopausal transition, the percentage of women with SPEQ scores indicating sexual dysfunction increased from 42% to 88%. Mood scores did not change significantly. In the early menopausal transition, women with low total SPEQ scores had lower estradiol level but similar androgen levels to those with higher scores. Decreasing SPEQ scores correlated with decreasing estradiol level but not with androgen levels. Hormone levels were not related to mood scores.

**Conclusion(s):** Female sexual functioning declines with the natural menopausal transition. This decline relates more to decreasing estradiol levels than to androgen levels. (Fertil Steril® 2002;77(Suppl 4):S42–8. ©2002 by American Society for Reproductive Medicine.)

**Key Words:** Androgens, menopause, testosterone, estrogen, sexual dysfunction, mood

The relative contribution of androgens and estrogen to female sexual functioning is controversial. Low libido, decreased well-being, blunted motivation, and fatigue are listed as major features of the proposed syndrome of female androgen deficiency (1, 2). However, defining and elucidating this syndrome has been problematic (3). First, the symptoms are vague and difficult to operationalize, and all can occur in other syndromes, such as major depressive disorder. In addition, there is no consensus on the definition of low testosterone levels. This lack reflects difficulties with assays and insufficient studies establishing the normal ranges of androgen levels in different life phases. Thus, no cut-off level for a normal range of testosterone has been agreed on (4).

What is known from studies of androgen levels in women of different ages and at different endocrine phases of life is that pronounced age-related and phase-related changes

in these hormones occur. Studies of hormone levels in women across the lifespan have been somewhat limited by their design: Most were cross-sectional and based on relatively small convenience or clinic samples with inherent biases. A notable exception is a study of the menopausal transition that used a population-based longitudinal design (5).

In addition, no comprehensive study has been done of a single cohort across the life cycle. It has also been difficult to synthesize the data in a meaningful way, because different assays with varying sensitivity, particularly for the lower end of the range, are used at different clinics (3).

What can be concluded from the data in women thus far is that testosterone levels reach an apparent peak in the early reproductive years (third decade of life) and then decrease with age. Women in their forties have approximately half the level of circulating total tes-

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tosterone as that of women in their twenties (6). The rate of the age-related decrease in total testosterone then seems to slow and is not specifically related to menopause (5). Dehydroepiandrosterone sulfate (DHEAS) shows similar changes to those described for testosterone but has an even more pronounced age-related decrease after the early reproductive years that continues through to later life (7, 8). Diurnal and menstrual cycle-linked changes in testosterone and androstenedione also occur (9). Testosterone (and androstenedione) levels are highest in the morning before 10:00 AM (10) and in the middle third of the menstrual cycle (11), although one small study (12) found that the midcycle ovarian increase in free testosterone level did not occur in older menstruating women (43–47 years of age).

If there is a clinical syndrome caused by androgen deficiency, observational studies should demonstrate lower levels of androgens, particularly free testosterone, among women with low levels of sexual functioning or diminished well-being. Methodologic problems, including the sensitivity of assays, lack of validated measures of sexual functioning, and the use of very small convenience samples (12, 13), limit the interpretation of previous studies. Some studies used daily ratings of sexual behavior (14, 15). Another major problem has been the lack of measurement of other confounding variables, which may vary along with androgens and may account for sexual behavior, which is the study end point. Thus, the finding of increased female sexual activity at midcycle, which correlates with increased free testosterone and androstenedione (15), may reflect the androgen increase in midcycle but may also reflect the midcycle estradiol peak. Because these studies measure associations, it is also possible that increased sexual activity during midcycle may increase testosterone levels.

Despite these limitations, most of these small observational studies (15–17) concur in finding a correlation between free and, in some cases, total testosterone levels and aspects of female sexual functioning, including frequency of sexual activities and female sexual interest or desire. In a study of 83 women, Floter et al. (18) found that on the questionnaire they used to assess sexual functioning, androstenedione correlated more strongly with sexual factors. Kaplan and Owett (13) compared 11 women with low androgen levels after chemotherapy or bilateral oophorectomy with 11 women in a similar hypoestrogenic state who had normal androgen levels. They found that all 11 women with low testosterone levels had markedly reduced sexual desire or fantasy, orgasm, and global sexual symptoms. Women with low testosterone levels were also significantly more likely to have decreased orgasm and global symptoms than were the control group of hypoestrogenic women.

Studies have also had contradictory findings and some seeming paradoxes. Eriksson et al. (19) found higher serum levels of free testosterone throughout the menstrual cycle in 11 women with premenstrual irritability and dysphoria com-

pared with 11 controls, suggesting a dysphoric effect of testosterone. Bachmann et al. (20), Cutler et al. (21), Schreiner-Engel et al. (22), Bancroft et al. (23), and Cawood and Bancroft (24) failed to find an association between androgen levels and sexual functioning. The last study did, however, find an association between DHEA and well-being.

Thus, while some small observational studies suggest a link between androgens and sexual functioning in women, there is no body of substantial evidence based on large samples and validated questionnaires to confirm these findings.

We previously found no significant change in positive (25) or negative mood scores (26) but did observe significant changes in female sexual functioning associated with the menopausal transition (27). As women passed through the menopausal transition, total scores on the Short Personal Experiences Questionnaire (SPEQ) and scores for the categories of sexual responsiveness, frequency of sexual activities, libido, and feelings toward the partner decreased significantly. A significant increase occurred in Vaginal Dyspareunia and Partner's Problems (Figs. 1 and 2) (27).

We have also used longitudinal analysis to elucidate the timing of changes in estradiol, FSH (28), and the free testosterone index (5) associated with the menopausal transition. No significant change in total testosterone or in DHEAS occurred with the menopausal transition, although aging itself had a significant effect on DHEAS levels (5).

We performed a longitudinal population-based cohort of Australian-born middle-aged women that used validated rating scales to determine whether androgen and estrogen levels are related to female sexual functioning and mood.

## MATERIALS AND METHODS

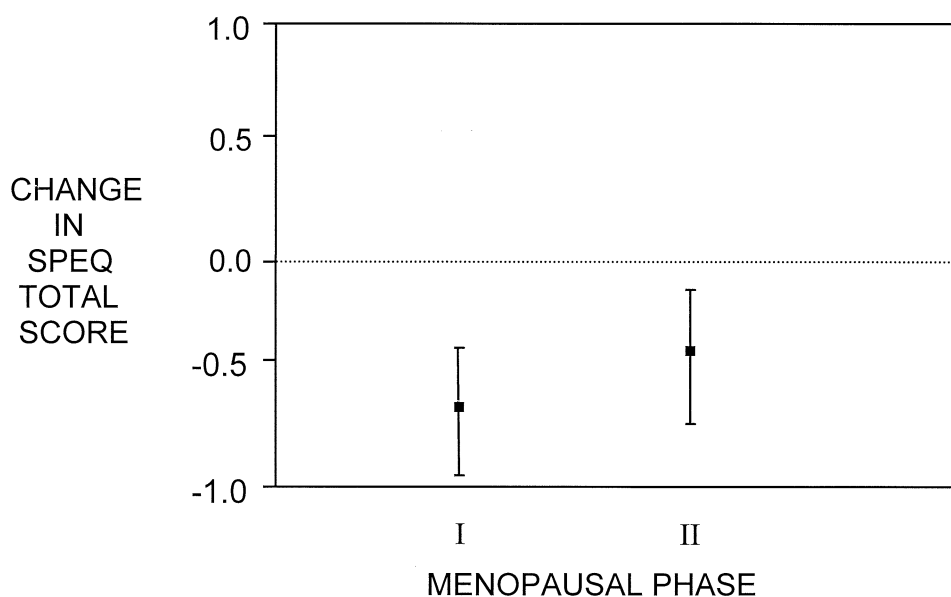
The Melbourne Women's Midlife Health Project is a prospective, population-based study of Australian-born women who were assessed annually for 8 years as they passed through the menopausal transition (27).

### Participants

The study began in 1991 with population sampling by random telephone digital dialing and baseline telephone interview of 2001 Australian-born women 45–55 years of age who lived in Melbourne (71% response rate) (29). All women at baseline who had experienced menses in the previous 3 months and were not taking the oral contraceptive pill or hormone therapy were invited to participate in a longitudinal study. Fifty-six percent of eligible women chose to participate (n=438). Volunteers for the longitudinal study were more likely than nonparticipants to report better self-rated health, paid employment, more than 12 years of education, having ever had a Papanicolaou smear, exercising at least once a week, and having undergone dilatation and curettage (30).

**FIGURE 1**

Change in total score on the Short Personal Experiences Questionnaire (SPEQ). Data are means; the bar indicates confidence intervals. I = change from early to late menopausal transition; II = change from late menopausal transition to postmenopause (27).



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The retention rate by year 8 of follow-up was 88%. Women were excluded from analyses if they dropped out, had surgical menopause during the study, took oral contraceptives or hormones during any study year, or did not complete the sexuality measure or blood sampling on the designated days. The sample available for repeated-measures linear regression was 226 participants.

### Measurements and Procedures

The study was approved by the Human Research Ethics Committee of the University of Melbourne, and the procedures followed were in accordance with the ethical standards of the National Health and Medical Research Council. All participants provided written informed consent for their participation in the study.

The Personal Experiences Questionnaire (PEQ) was based on the McCoy Female Sexuality Questionnaire (31), with modifications described elsewhere (32, 33). Women complete this questionnaire in their own homes. A fieldworker hands the questionnaire to each woman annually at the time of interview. The woman completes the questionnaire and hands it back to the fieldworker. Thus, only one Personal Experiences Questionnaire is completed each year. Items are meaned within each SPEQ factor, and a total score is calculated as the sum of SPEQ Factor 2 (sexual responsiveness), SPEQ Factor 3 (frequency of sexual activities), and

SPEQ Factor 4 (libido). On the basis of a clinical evaluative study of the SPEQ, an SPEQ total score of 7 or less is considered to indicate sexual dysfunction (36).

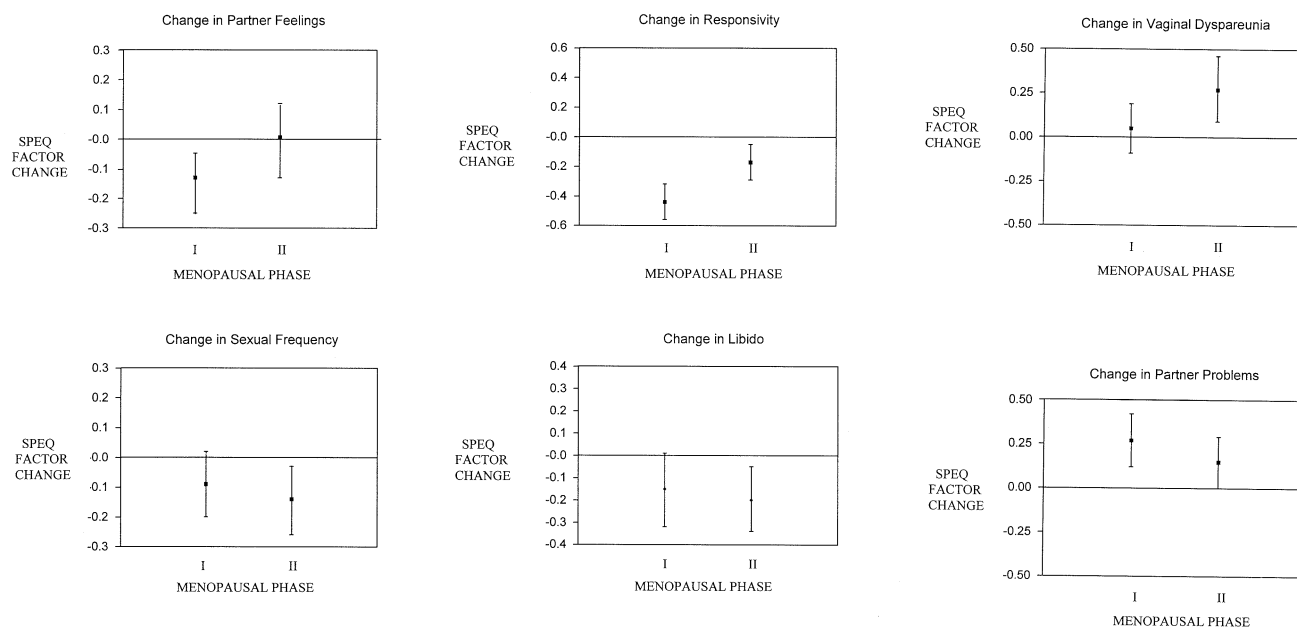
Mood scores were derived by using the Affectometer 2 (34), which was administered at annual interviews by the fieldworker. The Affectometer 2 has positive and negative mood subscales. Each scale contains 10 adjectives, and the score is the mean of the responses. In the current scale, women were asked whether they had felt the way they felt now most of the time, often, sometimes, or hardly ever (35). This differs from the system used by Kammann and Flett (34), who described five possible responses to each question. However, distributional characteristics and the degree of intercorrelation among the scores in our study were similar to those previously published (34, 35). The negative mood subscale correlates 0.83 with the Beck Depression Inventory (short form). Kammann and Flett (34) reported high reliability ( $\alpha$  value, 0.95).

Once a year, fasting morning blood samples for hormone radioimmunoassays were obtained between days 4 and 8 of the menstrual cycle from women who were still cycling or after 3 months of amenorrhea (30).

In year 1, FSH was measured by radioimmunoassay (RIA), as described elsewhere (30). In years 2 and 3, the automated Microparticulate Enzyme Immunoassay (Abbott

**FIGURE 2**

Changes in domains on the Short Personal Experiences Questionnaire (SPEQ). Data are means; the bar indicates confidence intervals. I = change from early to late menopausal transition; II = change from late perimenopause to postmenopause (27).



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Diagnostics IMX Analyser; Abbott Laboratories, Abbott Park, IL) was used, and from year 4 onward, the TOSOH AIA1200 automated Enzyme Immunoassay (Abbott Laboratories) was used. Correlation coefficients were 0.98 for FSH measured by the IMX system and RIA and 0.99 for FSH measured by the TOSOH system and the IMX system.

Estradiol was measured by using a double-antibody RIA kit purchased from Diagnostic Products Corp. (Diagnostics Product Corporation, Los Angeles, CA) Women younger than 39 years of age sampled between the fourth and seventh days of the cycle had serum FSH levels of 2.2–8.3 IU/L and estradiol levels of 150–500 pmol/L. Postmenopausal women had serum FSH levels > 22 IU/L. The free estradiol index was calculated as the ratio of measured estradiol to measured sex hormone-binding globulin (SHBG) × 100.

Serum testosterone was measured by using double-antibody RIA, after sample extraction and polyethylene glycol-enhanced separation of bound from free ligand with <sup>125</sup>I-iodinated testosterone as tracer. The between-assay coefficient of variation at a testosterone level of 2 nmol/L was 12%. The normal range for serum testosterone in healthy cycling women using this assay is 1.0–2.8 nmol/L at our laboratory. For year 8, testosterone was measured on the ACS180 (Bayer Corporation, Tarrytown, NY) system by using commercial reagents and calibrators from Bayer. The detection limit of this automated chemiluminescent enzyme

immunoassay was 0.3 nmol/L. On the basis of the correlation between results from this assay and the RIA, values obtained by using the ACS180 system were increased by 10% for the purposes of our study. The free testosterone index was calculated as the ratio of the measured testosterone to measured SHBG × 100. “Normal” values are quoted by the laboratory (Monash Medical Centre) as less than 4.1.

Sex hormone-binding globulin and DHEAS were measured with an automated chemiluminescent enzyme immunoassay (DPC) using the Immulite Automated Analyser (Immulite; Diagnostics Product Corporation, Los Angeles, CA). The reference range for SHBG at the Monash Medical Centre is 18 to 114 nmol/L, based on the in-house DPC reference range for nonpregnant women.

Menopausal status was determined by a change in menstrual status, which was asked at each annual interview in women who were not taking hormone therapy. Women who had menstruated in the previous 3 months were considered to have early menopausal transition. Women who reported at least 3 months of amenorrhea but less than 12 months of amenorrhea were considered to have late menopausal transition. Women were considered postmenopausal if they had had amenorrhea for at least 12 months. Fieldworkers verified reports of 3 or more months of amenorrhea from prospectively kept daily menstrual diaries.

TABLE 1

Hormone levels in the early menopausal transition at year 1.

Substance	SPEQ	SPEQ	P value
	total score $\leq 7$ (n = 63)	total score $> 7$ (n = 86)	
Testosterone (nmol/L)	1.42	1.43	.94
DHEAS ( $\mu\text{mol/L}$ )	2.20	2.23	.90
SHBG (nmol/L)	72.7	75.4	.65
Free testosterone index	1.95	1.89	.68
Estradiol (pmol/L)	222.5	298.2	.052
Free estradiol index	305.9	395.3	.080

Note: DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone-binding ; SPEQ = Short Personal Experiences Questionnaire.

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## Statistical Analysis

On the basis of evaluation of the SPEQ involving women with and without sexual dysfunction, an SPEQ total score  $\leq 7$  was considered to indicate sexual dysfunction (36). This test has a sensitivity and specificity of 79% (36). Total SPEQ scores were then calculated for menstruating women (early menopausal transition) in the first year of the longitudinal study and compared with SPEQ total scores for women who had reached postmenopausal status by year 8 of longitudinal follow-up. Total and domain scores on the SPEQ for each phase and years are given, along with corresponding hormone levels; the Student *t*-test was used for comparisons.

Repeated-measures linear regression was used to model total and domain scores on the SPEQ and mood scores as linear functions of age, log of free testosterone index and log of free estradiol index.

## RESULTS

At baseline, the women had a mean ( $\pm$ SD) age of  $48.5 \pm 2.3$  years. Thirty-seven percent had more than 12 years of education. The median parity was 3 (range, 0 to 9). Eighty-six percent of women were married or living with a partner in year 1, and 81% were married or living with a partner by year 8.

### Year 1

The mean age of early menopausal transition women in year 1 was  $49.1 \pm 2.25$  years. Of these women, 63 (42%) had a total SPEQ score  $\leq 7$  and 86 had scores  $> 7$ . Table 1 shows mean hormone levels in these women. The mean age of early menopausal transition women in year 1 was  $49.1 \pm 2.25$  years.

### Year 8

The mean age of women who were postmenopausal at year 8 was  $57.1 \pm 2.35$  years. Of these women, 137 (88%) had SPEQ scores  $\leq 7$ . Hormone levels did not differ be-

tween women with scores  $\leq 7$  and those with scores  $> 7$  at year 8, but most estradiol levels were below the level of sensitivity of the assay (20 pmol/L).

## Relationship of Changes in Hormone Levels to Changes in Sexual Functioning and Mood

Repeated-measures linear regression found that age ( $B = -.2$ ,  $P = .000$ ), log estradiol ( $B = .13$ ,  $P = .01$ ), and log free estradiol index ( $B = .12$ ,  $P = .014$ ) significantly affected total SPEQ score. Of the domain scores, sexual responsiveness was affected by age ( $B = -.07$ ,  $P = .000$ ) and log estradiol ( $B = .04$ ,  $P = .052$ ); frequency of sexual activities was affected by age only ( $B = -.05$ ,  $P = .000$ ), and libido was affected by age ( $B = -.45$ ,  $P = .000$ ), log estradiol ( $B = .087$ ,  $P = .001$ ), and log free estradiol index ( $B = .08$ ,  $P = .001$ ). No aspect of sexual functioning correlated with any of the androgens measured (total testosterone, free testosterone index, and DHEAS).

Neither positive or negative mood correlated with any of the hormones measured. In contrast, positive mood increased with age ( $B = .01$ ,  $P = .042$ ) and negative mood decreased with age ( $B = -.009$ ,  $P = .012$ ).

## DISCUSSION

Our study shows the extent of the change in sexual functioning associated with the menopausal transition. Forty-two percent of women in the early menopausal transition (at year 1 of follow-up) had SPEQ scores indicating sexual dysfunction, compared with 88% of postmenopausal women (at year 8 of follow-up). The decline in sexual functioning with the menopausal transition was also evident in a study based on menopausal phase without reference to year of study (27). This earlier study included control groups so that changes due to aging could be separated from those due to menopausal transition. Only the domain of sexual responsiveness showed a decline with both aging and the menopausal transition.

Decreasing androgen levels do not explain the dramatic decline in sexual functioning after menopause. As described elsewhere, the amount of bioavailable testosterone increases as women become postmenopausal because of the decrease in SHBG level (5).

We were able to examine only changes in sexual functioning during the menopausal transition. Because women were already older than 45 years of age at study entry, we could not examine changes in sexual functioning before the menopausal transition.

Nevertheless, androgen levels in these middle-aged women were already low. At the time that the assay was established, there was no diagnostic interest in low testosterone levels, and testosterone assays with the necessary sensitivity and precision to reliably define the lower end of the normal range in women are lacking. It is therefore

possible that assay insensitivity has contributed to the difficulty in establishing a correlation between androgens and sexual functioning.

Our study shows a relationship between low SPEQ scores in sexual functioning and low estradiol levels and between decline in estradiol and decline in sexual functioning ( $P=.05$ ). This analysis is limited by the floor effect in the estradiol assay and the statistical method used, which is not sophisticated enough to adequately define all aspects of change in estradiol level.

No direct relationship was found between mood scores and hormone levels in the early or late menopausal transition phases or between changing mood levels and changing hormone levels. In a previous analysis, we also found no direct effect of hormones or menopausal status on mood but did find that the menopausal transition has an indirect effect on negative mood scores, with increased vulnerability to stressors occurring at this time (26).

The current study involved only white women born in Australia. Most studies of hormones in middle-aged women have been done on Caucasian women in Australia, Europe, North America, and Scandinavia; thus, little information is available on differences by ethnicity. Recent findings from the Study of Women's Health Across the Nation, an observational study of middle-aged U.S. women of African, white, Chinese, Hispanic, and Japanese ethnicities, suggest that ethnic differences do exist. Further studies are urgently needed.

The evidence from double-blind, placebo-controlled clinical trials suggests androgens affect sexual functioning and mood. Most of these studies have been done in oophorectomized women, who have lost the important contribution of ovarian production to the total androgen pool and ovarian production of estrogens and progesterone. The incremental improvement of adding androgen to estrogen replacement has been assessed (37–39). These studies have found testosterone to have significant positive incremental effects over that of estrogen alone on mood and on aspects of sexual functioning. It was not clear whether testosterone acts physiologically or as a pharmacologic agent with a pronounced psychotropic effect. Whereas earlier trials used doses that were often above physiologic levels, later trials used lower doses of hormones similar to the upper end of laboratory ranges (40).

There have been relatively few negative trials, suggesting that whatever the effect of testosterone physiologically on mood and female sexuality, testosterone administration can have a powerful pharmacological effect. In a study of 280 healthy men and women 60–79 years of age, Baulieu and associates (41) found that daily administration of 50 mg of DHEA improved libido, skin status, and bone turnover in older women.

A randomized double-blind clinical trial also showed

**TABLE 2**

Hormone levels in Postmenopause at year 8.

Substance	SPEQ	SPEQ	P value
	total score $\leq 7$ (n = 137)	total score $> 7$ (n = 19)	
Testosterone (nmol/L)	1.05	1.05	.99
DHEAS ( $\mu$ mol/L)	1.75	2.07	.19
SHBG (nmol/L)	40.7	41.8	.77
Free testosterone index	2.52	2.52	.99
Estradiol (pmol/L)	27.4	29.1	.69
Free estradiol index	67.3	69.5	.88

Note: DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone-binding globulin; SPEQ = Short Personal Experience Questionnaire.

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significant positive effects of estrogen on mood and sexuality. A 12-month study was done in which 49 oophorectomized women received 3 months each of daily ethinyl estradiol, 0.05  $\mu$ m; levonorgestrel, 250  $\mu$ m; ethinyl estradiol plus norgestrel; and placebo in random order. No androgen comparison was included in the study design, but powerful effects of ethinyl estradiol on mood (42) and sexuality (43) were shown.

## CONCLUSIONS

Sexual functioning declines with the menopausal transition. Endogenous androgen levels do not seem to explain this decline, whereas estradiol has a significant relationship to declining sexual function. We previously showed the powerful effects of nonhormonal factors on sexual functioning in middle-aged women (44). Management of the middle-aged woman with sexual dissatisfaction must take all factors—psychological, physical (including hormonal), and relational—into account.

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