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ORIGINAL ARTICLE

Higher DHEA-S (dehydroepiandrosterone sulfate) levels are associated with depressive symptoms during the menopausal transition: results from the PENN Ovarian Aging Study

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Abstract The influence of sex hormones on mood during the menopausal transition has been the subject of ongoing investigation. Because dehydroepiandrosterone sulfate (DHEA-S) has been associated with several indicators of healthy aging, we conducted a population-based study of midlife women to determine the relationship between DHEA-S levels and depressive symptoms and major depression during the transition through menopause. Unexpectedly, the original report revealed a positive correlation between DHEA-S levels and depressive symptoms at baseline. The cohort was studied over 11 years to determine whether the positive association between DHEA-S levels and depression persists through the menopausal transition. We conducted a longitudinal cohort study with 11 assessments during an 11-year interval in Philadelphia, Pennsylvania, using a randomly identified, population-based sample of 436 African American and Caucasian premenopausal women aged 35 to 47 years at enrollment. For outcome measures, we used the Center for Epidemiologic Studies Depression Scale and standardized diagnosis of major depression. In a multivariable model, DHEA-S levels were positively associated with depressive symptoms when adjusted for age, menopausal stage, race, smoking status, and body mass index. There was no association between DHEA-S levels and a diagnosis of major depression. DHEA-S levels were positively associated with depressive symptoms through the menopausal transition. No association with major depression was apparent during the menopausal transition, but results may have limited power due to low prevalence of major depression in this cohort. These findings suggest that taking DHEA supplements may increase depressive symptoms for some women, and women and their physicians should be cautious about instituting DHEA replacement therapy during the menopausal transition.

Keywords Menopausal transition · Dehydroepiandrosterone sulfate · Depressive symptoms · Major depression · Longitudinal cohort

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Introduction

The adrenal androgen dehydroepiandrosterone sulfate (DHEA-S) is the most abundant circulating steroid in the body. Endogenous DHEA-S levels have been positively associated with several indicators of healthy aging. In the elderly, low DHEA-S levels have been associated with functional decline, elevated depressive symptoms, and cognitive impairment, although some investigators believe these associations only apply to men (Goldman and Glei 2007). Other studies of elderly women demonstrated a positive association between higher DHEA-S levels and improved activities of daily living (Fukai et al. 2009), insulin sensitivity (reflecting decreased risk of diabetes) (Casson et al. 2010), and lower depressive symptoms (Morsink et al. 2007).

The understanding of healthy aging has increasingly focused on midlife when many chronic diseases start. Several current longitudinal studies, the PENN Ovarian Aging Study (POAS) and the Study of Women's Health Across the Nation (SWAN) (Lasley et al. 2002), are characterizing the trajectories of sex steroids and their fluctuations in mid-life women, from the late reproductive years to postmenopause. While it is well documented that circulating levels of DHEA-S decline approximately 2% per year with normal aging (Lasley et al. 2002), the SWAN study found that more than 84% of women experiencing a progressive increase in DHEA-S levels in the menopause transition, i.e., from premenopause to early postmenopause (Crawford et al. 2009).

Although several studies suggest that DHEA-S and DHEA, the desulfated form of DHEA-S, appear to be important in the regulation of mood, the findings are inconsistent (Harsh et al. 2009; Maninger et al. 2009; Tichomirowa et al. 2005; Wolkowitz et al. 1997). Exogenous DHEA had antidepressant effects in adults of both sexes (Wolkowitz et al. 1999; Schmidt et al. 2005), but the studies are small and the mechanism of this antidepressant effect is unclear. In a clinic-based study, women ages 40–55, with new onset major or minor perimenopausal depression, were found to have lower DHEA-S and DHEA levels compared with matched non-depressed women (Schmidt et al. 2002). However, in two longitudinal, community-based studies of women in the menopausal transition, there was no significant association between endogenous DHEA-S levels and depressive symptoms (Bromberger et al. 2010; Dennerstein et al. 2002), although a longitudinal association was found between higher testosterone (DHEA metabolite) levels and elevated depressive symptoms in the Study of Women's Health Across the Nation (SWAN) (Bromberger et al. 2010). Neither study determined associations between DHEA-S levels and major depression.

We previously conducted a cross-sectional analysis at enrollment in the POAS cohort that demonstrated a positive association between DHEA-S levels and depressive symptoms in late reproductive age women (Morrison et al. 2001). The study also showed that higher DHEA-S levels were associated with depressive symptoms in the younger group, and lower levels of DHEA-S were associated with depressive symptoms in the older group.

In the present study, we followed women in the POAS cohort for 11 years to confirm prospectively the association of DHEA-S levels and depressive symptoms as women progressed through the menopausal transition. We planned to investigate prospectively the association of DHEA-S levels and depressive symptoms by age group. As a secondary aim, due to power limitations, we planned to study whether DHEA-S levels were associated with a diagnosis of major depression (MDD) during the menopausal transition. We hypothesized that the relationship of DHEA-S and major depression would be positive, similar to the relationship of DHEA-S and depressive symptoms.

Methods

Cohort The population-based cohort of 436 women was identified by random digit dialing to households in Philadelphia County as previously described and enrolled equal numbers of African American and Caucasian women (Morrison et al. 2001). Eligibility criteria included 35 to 47 years of age, menstrual cycle length in normal range (22–35 days) during the previous 3 months, and at least one ovary plus intact uterus. Exclusion criteria included current use of psychotropic or hormonal medications, pregnancy or breastfeeding, serious health problems known to compromise ovarian function, alcohol or drug abuse within the previous year, and non-English speaking. The study was approved by the University of Pennsylvania Institutional Review Board and written informed consent was obtained from the participants.

Study design Data were collected in 11 assessment periods over 11 years. The first six periods were at 8–9-month intervals, and periods 7–10 were at annual intervals, with a 2-year gap between periods 10 and 11. Each assessment period had two visits, scheduled at the participant's home, between days 1 and 6 of two consecutive menstrual cycles (or a 1-month interval in non-cycling women) in order to obtain interview, questionnaire, anthropometric measures, and blood samples for hormone assays. At the 11th assessment period, 131 women had withdrawn for the following reasons: withdrew consent (n=21), lost to follow-up (n=40), time constraints (n=10), medical or personal

problems (n=9), moved from area (n=9), no reason given (n=31), and deceased (n=11).

Study measures All data were obtained by trained research interviewers in individual in-person interviews. The structured interview, which was repeated at each assessment, focused on overall health and included demographic information, menstrual cycle dates, reproductive history, general health status, and behaviors (including smoking, alcohol, and medications used). Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977). Scores were used as a continuous variable, with higher CES-D scores representing more depressive symptoms. The Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al. 1994) was used in assessment periods 1–6, and the Patient Health Questionnaire, which was developed and validated from the PRIME-MD, was used in periods 7–11 to determine DSM-IV diagnosis of Major Depression (MDD) (Spitzer et al. 1999). Age was dichotomized into two age groups based on the mean age at the baseline visit. Definitions of menopausal stage (Gracia et al. 2005) were adapted from the STRAW (Staging System for Reproductive Aging Women) criteria (Soules et al. 2001) and have shown significant associations with changes in reproductive hormones (Freeman et al. 2005). At each assessment, the participant was assigned to a menopausal stage, based on the bleeding patterns at that assessment: (1) *premenopausal*, regular menstrual cycles in the 22–35-day range, with no change in cycle length; (2) late premenopausal, one cycle change of ≥7 days compared to her enrollment cycle length at baseline; (3) early transition, changes in cycle length of ≥7 days in either direction from the participant's personal baseline at enrollment in the cohort, observed for at least two consecutive cycles in the study or 60 days of amenorrhea; (4) late transition, 90 days to 11 months of amenorrhea during the study; and (5) postmenopausal, ≥12 months of amenorrhea.

Other variables reported to have associations with DHEA-S were included as covariates: race (lower DHEA-S levels in African American women compared with Caucasian women) (Girgis et al. 2000; Morrison et al. 2001), current smoking (associated with increased DHEA-S levels) (Lasley et al. 2002; Khaw et al. 1988), body mass index (BMI) (positively associated with DHEA-S levels; Mazza et al. 1999) (inversely associated with DHEA-S levels; Burger et al. 2000) (inversely associated with DHEA-S levels, except in Japanese American women, positively associated; Lasley et al. 2002), and current alcohol use (Randolph et al. 2003; Rinaldi et al. 2006). Testosterone levels and estradiol levels were added separately to the final model to investigate whether the relationship between DHEA-S and mood was influenced by these DHEA metabolites.

Non-fasting blood samples for the hormone assays were collected between days 1 and 6 of the menstrual cycle in two consecutive cycles (or 1 month apart in non-cycling women) at each of the 11 assessment periods for a possible total of 22 samples per subject. Blood samples were taken between 10 AM and 7 PM, centrifuged, and frozen in aliquots at −80°C. Assays of serum levels of DHEA-S, testosterone, and estradiol were measured at each assessment by radioimmunoassay in the General Clinical Research Center using commercial kits (Coat-a Count; Diagnostic Products, Los Angeles, CA, USA). The assays were batched and run only for this cohort. All assays were performed in duplicate and repeated if the values differed by more than 15%. The inter-assay and intra-assay coefficients of variation were consistently less than 5% (with lower coefficients reflecting better hormone reproducibility). The means of the duplicates were used for the analysis.

Statistical analysis The full cohort was included in the analysis. A general linear mixed regression model for repeated measures was used to estimate the unadjusted and adjusted associations of each study variable with the CES-D score as a continuous variable and MDD as a dichotomous variable. Results were summarized using odds ratios with 95% confidence intervals for categorical variables and regression coefficients (slopes) for continuous measures. The distribution of continuous CES-D scores was examined at each assessment period to assure that normality assumptions were met. A natural logarithm transformation of hormone levels was used in all analyses to accommodate modeling assumptions and reduce the influence of skewed data.

For each type of model, we assumed that the repeated outcomes for each woman were correlated. Robust statistical tests for the associations of interest were adjusted using generalized estimating equation (GEE) methodology (Zeger et al. 1988). Reproductive hormone levels and all other covariates associated with depression status in the unadjusted analyses at p <0.20 were included in the model selection process for the multivariable models. The final selection of covariates was guided by whether each variable remained statistically significant at $p \leq 0.05$ or whether its inclusion modified other significant associations in the model by 15% or more (Maldonado and Greenland 1993). All available data for each participant were included in the repeated measures models. Observations during pregnancy, breastfeeding, hormone use, current psychotropic use, and use of medications associated with altered DHEA-S levels were censored at the times of their occurrence. Hormone measurements taken after a participant reported

hysterectomy, oophorectomy, or cancer were set to missing from occurrence onward.

Comparison of baseline data between participants who continued throughout the study and dropouts revealed no significant differences in the study variables: age, history of depression, DHEA-S level, race, smoking history, body mass index, hot flashes, educational level, and income level. Post hoc calculations determined that this study had 80% power to detect a difference in natural log DHEA-S (ln[DHEA-S]) between subjects with major depression compared to those without major depression for a one standard deviation (0.7) difference between these groups. This amount represents a change in DHEA-S levels of 16% or more. The SAS statistical software package, version 9.1, was used for all analyses. Statistical tests were two-tailed with $p \leq 0.05$ considered significant.

Results

Table 1 shows subject information at the 11-year endpoint. The mean age was 50.6 years (standard deviation, SD, 3.5 years); 47.3% were African American and 52.7% were Caucasian; 33% of the cohort was postmenopausal, 59% were in the menopausal transition, 2% were premenopausal, and 6% had a hysterectomy and/or oophorectomy. Mean DHEA-S levels decreased 13% from baseline levels at the 11-year time point.

Table 1 Characteristics of POAS cohort at 11th assessment

	11th Assessment $N=300$[a] Mean value (SD) or N (%)
Age	50.6 (3.5)
Race	
Caucasian	158 (52.7%)
African American	142 (47.3%)
Menopausal stages	
Premenopausal	6 (2.0%)
Late premenopause	9 (3.0%)
Early transition	106 (35.3%)
Late transition	62 (20.7%)
Postmenopause	100 (33.3%)
Hysterectomy or oophorectomy	17 (5.7%)
Depressive symptoms (CES-D scores)	11.6 (9.6)
Current major depression	16/298[b] (5.4%)
DHEA-S levels (μg/dL)	92.3 (56.5) $N=294$
Current smoking	95 (31.7%)
BMI	31.4 (8.7) $N=284$

[a] Five subjects were missing at assessment 11

[b] Two subjects did not have the assessment performed

DHEA-S levels and depressive symptoms DHEA-S levels were positively associated with depressive symptoms (CES-D scores) in the longitudinal analysis in both unadjusted (estimate=1.21, $p=0.007$) and adjusted analyses (estimate=1.07, $p=0.013$). Covariates did not affect this association; the covariates were independently associated with depressive symptoms as shown in Table 2. There was no significant interaction between DHEA-S level and depressive symptoms by age group (>41 years, ≤41 years), indicating that the positive association between DHEAS and depressive symptoms did not differ between the younger and older women in the cohort (data not shown). There was also no significant interaction between DHEAS and race, indicating that the association between DHEAS and depressive symptoms did not differ between African American and white women.

Influence of testosterone and estradiol on final model The individual addition of either testosterone levels or estradiol levels to the final model did not alter the observed relationship between DHEA-S and CES-D scores (Table 2). Both testosterone and estradiol are metabolites of DHEA. With univariate analysis, testosterone levels were inversely related to CES-D scores (estimate=−0.40, $p=0.02$) and estradiol levels were not significantly related to CES-D scores. When levels of testosterone and estradiol were added to the multivariable model separately, neither were significantly related to CES-D scores nor did they significantly impact the estimate (adjusted) for the DHEA-S and depressive symptoms relationship (data not shown).

DHEA-S levels and major depression DHEA-S levels were not associated with MDD (Table 3). The diagnosis of MDD was not associated with levels of testosterone or estradiol in univariate analysis or multivariate analysis.

Menopausal stage and other covariates Other covariates in the model did not impact the association of DHEA-S and depressive symptoms in general, but several were independently associated with CES-D scores (Table 2). Generally, the transition through menopause was associated with lower depressive symptoms scores when compared with premenopause. Similarly, the odds of major depression decreased as well during the menopausal transition. BMI had a trend association with CES-D scores in the unadjusted model (estimate=−0.08, $p=0.059$), but not the adjusted model. When BMI was removed from the model, the adjusted estimate for the association of

Table 2 Estimated associations with depressive symptoms (CES-D) from the univariate and final multivariable model

Variables	Unadjusted estimate	Adjusted estimate	95% Confidence limits for adjusted estimate	*p* value for adjusted estimate
Natural log of mean DHEA-S level	1.21**	1.07	0.22, 1.91	0.013*
Menopausal status[a]	Unadjusted $p \leq 0.0001$****			Adjusted $p \leq 0.0001$****
Premenopause	Reference	Reference	Reference	
Late premenopause	−0.94*	−0.42	−1.26, 0.43	0.33
Early transition perimenopause	−2.30****	−1.18	−1.98, −0.38	0.004**
Late transition perimenopause	−2.35****	−1.48	−2.68, −0.27	0.016*
Postmenopause	−4.41****	−3.32	−4.71, −1.92	<0.0001****
Age >41	−3.64****	−2.78	−3.86, −1.71	<0.0001****
Race group African American	2.65***	2.95	1.41, 4.48	0.0002***
Smoker	2.58****	1.66	0.56, 2.77	0.003**
Body mass index	−0.08 $p=0.059$	−0.04	−0.12, 0.03	0.26
Natural log of mean testosterone levels[b]	−0.40*	−0.17	−0.55, 0.20	0.37
Natural log of mean estradiol levels[b]	0.20	−0.06	−0.47, 0.34	0.76

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$

[a] Five categories representing menopausal status are incorporated in the model using four indicator variables (four degrees of freedom)

[b] Not included in baseline multivariable model, only included to measure metabolite effect

DHEA-S and depressive symptoms decreased to 0.83 suggesting that BMI is a confounder of the relationship between DHEA-S levels and depression. Alcohol use was included as a covariate, but was not significantly associated with CES-D scores, nor did it affect the relationship between DHEA-S levels and depressive symptoms (estimate=1.08, $p=0.01$).

Discussion

This report found a positive association between plasma DHEA-S levels and depressive symptoms through the menopausal transition. The longitudinal data confirm the overall findings of our cross-sectional analysis that was conducted at cohort enrollment when women were

Table 3 Odds ratios for associations with diagnosis of major depression from the univariate and final multivariable model

Variables	Unadjusted odds ratio	Adjusted odds ratio	95% Confidence limits for adjusted odds ratio	*p* value for adjusted odds ratio
Natural log of mean DHEA-S level	0.99	0.95	0.72, 1.26	0.72
Menopausal status[a]	Unadjusted $p \leq 0.0001$****			Adjusted $p=0.0002$***
Premenopause	Reference	Reference	Reference	
Late premenopause	1.23	1.20	0.84, 1.70	0.32
Early transition perimenopause	0.63**	0.70	0.47, 1.04	0.07
Late transition perimenopause	0.28***	0.27	0.15, 0.64	0.006**
Postmenopause	0.35**	0.39	0.15, 1.01	0.053
Age >41	0.52****	0.67	0.47, 0.96	0.029*
Race group African American	2.50****	2.14	1.37, 3.36	0.0009***
Smoker	1.98***	1.78	1.23, 2.61	0.002**
Body mass index	1.02*	1.03	1.01, 1.05	0.01**
Natural log of mean testosterone levels[b]	1.01	1.05	0.88, 1.24	0.61
Natural log of mean estradiol levels[b]	1.05	1.06	0.85, 1.32	0.60

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$

[a] Five categories representing menopausal status are incorporated in the model using four indicator variables (four degrees of freedom)

[b] Not included in baseline multivariable model, only included to measure metabolite effect

premenopausal (Morrison et al. 2001). However, these finding contrast those of two other longitudinal studies that found no significant association between DHEA-S levels and depressive symptoms in perimenopausal women (Dennerstein et al. 2002; Bromberger et al. 2010). Methodological differences, such as different measures of depressed mood in the study of Dennerstein et al. and differences in menopausal status at study baselines, may contribute to these conflicting findings. It is also possible that the association of DHEA-S levels and depressive symptoms during the transition to menopause was obscured by a substantial proportion of the cohort having a baseline in perimenopause rather than the premenopausal baseline of the present study (Dennerstein et al. 2002; Bromberger et al. 2010).

There was no significant association of testosterone or estradiol levels with depressive symptoms in our cohort, and the inclusion of these hormones in the multivariable models did not change the association between DHEA-S and depressive symptoms. In contrast, the SWAN cohort showed no relationship between depressive symptoms and DHEA-S, but did show a positive association between both total and free testosterone levels and depressive symptoms (Bromberger et al. 2010). Reasons for these differences are not clear, but could be due to methodological differences in hormone assessments (Rosner et al. 2007) or differences in the populations studied (the large SWAN cohort included women of Chinese, Japanese, and Hispanic ethnicities—Bromberger et al. 2010—who were not included in the POAS cohort), and further studies are needed.

Our previous cross-sectional analysis suggested age-dependent differences in the relationship of DHEA-S levels and depressive symptoms when the cohort was premenopausal. This was not confirmed in the present study where the positive association between DHEA-S and depressive symptoms did not differ by age group as the women progressed through the menopausal transition. Some cross-sectional, community-based studies in African American middle-aged (but not menopausal transition) (Haren et al. 2007) and geriatric (Barrett-Connor et al. 1999; Morsink et al. 2007) women have suggested either no relationship or an inverse relationship between DHEA-S levels and depressive symptoms. None of these studies focused on women during the menopausal transition. One longitudinal study of DHEA-S levels in women during the menopausal transition (ages 50–60) found DHEA-S levels associated with cardiovascular risk factors (Johannes et al. 1999). We suspect that different findings of DHEA-S levels and depressive symptoms during the menopausal transition may reflect physiological differences that are not well understood. Our findings do not support the notion of higher DHEA-S levels being a marker for healthy aging (improved mood) in menopausal women.

The 11-year length of the present study offered an opportunity to observe women during an episode of major depression. However, we found no association of DHEA-S levels and major depression in our cohort. Such an association has been noted in studies of non-menopausal clinical populations (male and female) with major depression (Takebayashi et al. 1998; Assies et al. 2004). Moreover, successful treatment of depression was followed by reductions in both DHEA-S levels (Takebayashi et al. 1998; Fabian et al. 2001) and DHEA levels (Fabian et al. 2001). Although post hoc power calculations determined that this study had 80% power to detect a difference in DHEA-S levels in women with MDD compared to those without of 16% or more, it is possible that the power was not adequate to detect it a weak association between DHEAS and MDD if it existed in this cohort.

The significant association of DHEAS with depressive symptoms in the menopausal transition may represent an independent neuropsychiatric phenomenon (such as a distinct subsyndromal depressive disorder) from major depression. Thus, an elevated DHEA-S level during the perimenopausal transition may represent a causal factor for subsyndromal depressions during perimenopause. This is seen in geriatric populations, in whom there is an increase in the prevalence of subsyndromal depressions and a decrease in the prevalence of major depression, and subsyndromal depressive disorders and major depression appear to be independent phenomena (Gurland 2004). In our cohort of African American and white women, BMI was a confounder of the association of DHEAS with depressive symptoms and explained approximately 20% of the relationship between DHEA-S and depressive symptoms.

Mechanism of the DHEA-S association with depression

Although DHEA-S and DHEA are commonly referred to as steroid hormones, neither has a known receptor. DHEA can be converted to testosterone and estradiol, which could exert effects on mood. However, the association between DHEA-S and depressive symptoms in our cohort does not appear to be mediated by systemic levels of these metabolites. When testosterone and estradiol were added to the multivariable model separately, neither affected the observed association between DHEA-S levels and depression. Other metabolites of DHEA-S, such as estrone, were not measured and could explain the association of DHEA-S levels and depressive symptoms. Another mechanism by which elevated DHEA-S levels might be associated with depressive symptoms is by potentiating the action of glutamate at the *N*-methyl-D-aspartate (NMDA) receptor, which has been proposed as an important element in the final common pathway of antidepressant action (Paul and Skolnick 2003). The NMDA antagonist ketamine produced a rapid antidepressant effect in patients with major depressive disorder

(Zarate et al. 2006). The mechanism has been postulated to involve an increase in the ratio of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) vs. NMDA glutamatergic transmission (Maeng and Zarate 2007). Conversely, drugs that decrease AMPA or increase NMDA glutamatergic transmission might be expected to worsen depression. DHEA-S is thought to be a positive allosteric modulator of the NMDA glutamate receptor in the hippocampus because it blocks the binding of the NMDA inhibitor ifenprodil to the NR2B subunit (Johansson and Le Grevès 2005), and thus may exert its effects on mood through NMDA glutamatergic activation. Regardless of the mechanism, it is possible that in some women, exogenous DHEA, which does not require a prescription in the USA, could trigger depressive symptoms during the menopausal transition.

Limitations Only generally healthy women who were ages 35–58 years during the study interval and in the menopausal transition were evaluated and only two racial/ethnic groups were represented. Thus, the positive association between DHEA-S levels and depressive symptoms may not apply to other age groups, different ethnic/racial groups, or men. While the positive association of DHEA-S and depressive symptoms is statistically significant, it is not strong. This is possibly influenced by obtaining DHEA-S levels throughout the day, inasmuch as late-day samples may be lower than those obtained earlier in the day (Assies et al. 2004; Carlström et al. 2002). However, these diurnal fluctuations in DHEA-S levels are generally considered clinically insignificant because they are minor and probably related to serum albumin levels (Carlström et al. 2002). It is possible that the association between DHEA-S and depressive symptoms was mediated through testosterone, but not detected due to assay sensitivity; the standard radioimmunoassay of testosterone may be less reliable for measuring very low levels of this hormone (Rosner et al. 2007).

Summary The present study demonstrated a positive association between levels of DHEA-S, an abundant adrenal steroid hormone, and depressive symptoms in healthy women in the menopause transition. Our study also shows that this association between DHEA-S and depressive symptoms persists through the menopausal transition. These findings suggest that taking DHEA supplements may increase depressive symptoms for some women, and women and their physicians should be cautious about instituting DHEA replacement therapy during the menopausal transition.

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