Effects of Oral vs Transdermal Estrogen Therapy on Sexual Function in Early Postmenopause: Results from the Kronos Early Estrogen Prevention Study (KEEPS).

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Abstract

Importance: Sexual function is an important aspect of women's health. Sexual dysfunction associated with declining estrogen levels around the menopausal transition can lead to distress and reduction in the quality of life.

Objective: To determine the differential effects of oral versus transdermal estrogen therapy on various aspects of sexual function over time in recently postmenopausal women.

Design: Ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS), a prospective, randomized, double-blinded, placebo-controlled trial of menopausal hormone therapy (MHT) in healthy menopausal women within 3 years of their last menstrual period (LMP). Participants were followed for 4 years from time of randomization.

Setting: Multi-center study.

Participants: Of the 727 KEEPS enrollees, 670 participated in this ancillary study. Women were between 42 and 58 years old with intact uteri, and between 6 to 36 months from LMP, with plasma follicle-stimulating hormone (FSH) level ≥35 ng/mL and/or estradiol (E_2) levels <40 pg/mL, and with no history of severe psychiatric illness or cardiovascular disease.

Intervention(s) for clinical trials or Exposure(s) for observational studies: Women were randomized in a ratio of 4:4:5 to either 0.45 mg/d oral conjugated equine estrogens (o-CEE) or 50 mcg/d transdermal 17β-E_2 (t-E_2), or placebo. In addition, participants also received 200 mg oral micronized progesterone (if randomized to o-CEE or t-E_2) or placebo (if randomized to placebo estrogens) for 12 days each month.

Main Outcome(s) and Measure(s): Key aspects of sexual function and experience (desire, arousal, lubrication, orgasm, satisfaction and pain) were assessed at baseline, 18, 36 and 48 months, utilizing a validated tool, the Female Sexual Function Inventory (FSFI). Scores for individual domains and overall FSFI score, as well as Female Sexual Dysfunction (FSD, defined as a combined FSFI score less than 26.55) were determined and compared longitudenally among groups.

Results: 72.9% of KEEPS-sexual function participants had FSD. Transdermal E_2 treatment was associated with significant improvements in the FSFI total score across all time points compared to placebo among all participants (average efficacy: 2.6, 95% CI: 1.11 – 4.10; p=0.0007), which was supported by significant changes in physical aspects of sexual function including increased lubrication (0.61, 95% CI 0.25 -0.97, p=0.0009) and decreased pain (0.67, 95% CI 0.25 – 1.09, p=0.002). Significant improvements were consistently observed at 18 months of t-E_2 treatment relative to placebo ($p<0.038$) in all other domains, and relative to o-CEE in desire, arousal, and FSFI scores ($p<0.022$). The odds of FSD were significantly reduced at 18 and 48 months of t-E_2 treatment (OR=0.64, 95% CI 0.42 – 0.98; p=0.04 and OR =0.57, 95% CI 0.36 – 0.91; p=0.02, respectively). Age and FSD moderated the treatment effect of t-E_2. The effect of t-E_2 on sexual function was significantly greater in women with FSD as compared to women without FSD at 18 and 36 months of treatment ($p<0.04$). Older age at baseline was associated with less benefit from

t-E_2 treatment at 36 month and 48 month (both p=0.03). For o-CEE, lubrication, pain, satisfaction and FSFI total scores increased significantly only at 36 months of treatment relative to placebo (p<0.03), with no significant reduction in the odds of FSD.

Conclusions and Relevance: Although both formulations demonstrate benefits for sexual function in early postmenopausal women, t-E_2 treatment was more effective than o-CEE especially in the subset of women with FSD, which make up the majority of our study population. Because the efficacy declines with age, early t-E_2 intervention is recommended for postmenopausal women with FSD.

Trial Registration: NCT00154180.

Introduction

Hypoestrogenemia is the endocrine hallmark of menopause and is characterized by 5 to 10 fold reduction in circulating levels of estradiol (E_2).[1] This reduction in estrogen has profound structural and functional effects on estrogen-responsive tissues that mediate female sexual response, including reduction in volume and thinning of the skin of external genitalia (i.e., labia minora, labia majora, clitoris), reduced elasticity and depth of the lamina propria, thinning of stratified squamous epithelium of the vagina, loss of subcutaneous fat, and parallel involution of the clitoral corpora cavernosa.[2,3] Whereas these anatomical changes result in decreased surface area available for sensual stimulation and lubrication, low E_2 levels are associated with reduced overall blood flow to female genitalia, leading to attenuated genital vasocongestion during sexual intercourse. Over time, hypogonadism results in vaginal dryness and dyspareunia.[4] Estradiol is also a modulator of serotonergic function as it affects regions of the brain known to regulate

mood and desire, including the amygdala, hippocampus, and the hypothalamus.[5] Hypoestrogenism is associated with altered mood, sleep and cognition, all of which may have direct or indirect effects on sexual function.[1,6] Menopausal women indeed have an increased incidence of sexual disorders[7-9] and at least 23% of naturally menopausal women report to be distressed by their low sexual desire.[10] Conversely, midlife women with higher levels of enjoyment from sexual activity report a higher sense of purpose in life.[11]

A recent meta-analysis revealed that treatment with estrogens alone or in combination with progestogens was associated with a small to moderate improvement in sexual function, (particularly in pain), when used in women with menopausal symptoms or in early postmenopause (i.e., within five years of amenorrhea).[12] Though the analysis included stratification by time since menopause, it did not stratify by the route/composition of estrogens used, potentially due to the lack of large, prospective, randomized trials comparing these different treatment regimens. Varying pharmacokinetics may affect the efficacy of hormone therapy (rev.[13]), as oral estrogens are subject to extensive hepatic metabolism and result in serum estrone (E_1, the major component of o-CEE) to estradiol ratio of approximately 5:1 to 7:1. In contrast, transdermal estrogen bypasses hepatic metabolism and results in a steady-state concentration of estradiol with an E_1/E_2 ratio of 1:1, approximating that seen prior to menopause.[14] Additionally, hepatic production of sex hormone binding globulin (SHBG) is induced by oral estrogens, resulting in a decline in free (bioavailable) estrogens and androgens. Indeed, plasma concentration of free E_2 with t-E_2 is twice that seen with oral formulations.[15]

The Kronos Early Estrogen Replacement Study (KEEPS) was a prospective, randomized, double-blinded, placebo-controlled trial originally designed to test whether estrogen reduces

progression of atherosclerosis when initiated *early* in postmenopause (i.e., within 36 months of the last menstrual period, LMP).[16] In KEEPS, transdermal 17β-estradiol was directly compared with oral conjugated equine estrogens to determine whether both have an equivalent effect on menopause-associated morbidities.[17] The current KEEPS Sexual Function ancillary study was undertaken to examine changes in sexual function over time in recently postmenopausal women randomized to either o-CEE or t-E_2 therapies for a period of four years.

The unique timing relative to menopause onset for initiation of hormone therapy, along with selection criteria for a healthy cohort closer to the mean age of menopause, make this study population especially suitable for assessment of sexual function while minimizing potential confounders related to aging, such as menopause-associated urogynecological and psychological comorbidities (i.e., uterovaginal prolapse, urinary tract symptoms, depression), as well as cardiovascular risks, which were previously shown to be associated with sexual dysfunction.[3,18-20]

Methods

Menopausal women who were within 3 years of their final menstrual period from nine recruitment sites across the United States participated in the KEEPS. The trial began in July 2005 with complete enrollment of 727 participants in the parent trial by June 2008.[21] All women provided written informed consent and institutional review boards at participating sites approved the study procedures. A detailed description of volunteer recruitment, participating clinical study centers, inclusion/exclusion criteria, safety monitoring, randomization and blinding protocols for KEEPS have been published elsewhere.[21-23] In brief, eligible women were between 42 and 58 years of age who were at least 6 months and no more than 36 months from LMP, with plasma

follicle-stimulating hormone (FSH) level ≥35 ng/mL and/or E_2 levels <40 pg/mL. Women excluded from the study were those who had undergone hysterectomy or surgically-induced menopause, abnormal mammogram, severe psychiatric illness including untreated major depression, a history of clinical cardiovascular disease including myocardial infarction, angina, congestive heart failure, or thromboembolic disease, those with coronary artery calcification with Agatston score ≥50 U (indicating significant subclinical coronary artery disease), as well as current moderate or heavy smoking (more than ten cigarettes/day by self-report), severe obesity [body mass index (BMI) >35 kg/m^2], dyslipidemia (LDL cholesterol >190 mg/dL), hypertriglyceridemia (triglycerides >400 mg/dL), uncontrolled hypertension (systolic blood pressure >150 mm Hg and/or diastolic blood pressure >95 mm Hg) or fasting glucose >126 mg/dL.

Eligible KEEPS participants were randomized in a ratio of 4:4:5 to either daily 0.45 mg oral o-CEE with 200 mg micronized progesterone for 12 days each month, 50 mcg daily t-E_2 with 200 mg micronized progesterone for 12 days each month, or placebo pills and patches. Six hundred and seventy of the 727 KEEPS enrollees agreed to participate in the sexual function ancillary study (n=209 in the o-CEE group; n=204 in the t-E_2 group and n=257 in the placebo group). Sexual function data were collected at four of the parent study visits: baseline, and months 18, 36, and 48. Participants completed the FSFI questionnaire, a well validated tool assessing the key dimensions of sexual function along six domains of sexual function, including desire, arousal, lubrication, orgasm, satisfaction and pain.[24,25] In brief, each domain has a score range that, when multiplied by a domain-specific factor, gives the individual domain score. The full FSFI scale

score equals the sum of the six domain scores with higher scores reflecting better sexual function.

Statistical analysis

Descriptive analyses were conducted to summarize the participants' demographics and clinical characteristics at baseline. Chi-square test for categorical variable and analysis of covariance (ANOVA) were used to examine whether the treatment groups were comparable at baseline because this trial was ancillary to parent randomized study. Mixed model repeated measures analysis was used primarily to evaluate the efficacy of treatments. The approach proposed by Fitzmaurice et al.[26] was used. The unstructured covariance matrix was used to account for the correlation between repeated assessments within same individual. Time and group interaction was included as main effect. Linear contrasts were performed to compare the change from baseline at each time point across groups. The advantage of this approach included the use of maximum likelihood method for statistical efficiency and the capacity to use all available data to handle missing values.[27] Duration of menopause prior to enrollment, age at enrollment, history of menopausal hormone treatment, education, ethnicity and income were included in covariate adjustment because those variables are either conceptual confounders or associated with missing data. The primary analysis was to evaluate the overall efficacy of o-CEE and t-E_2 on improvement in FSFI sum scores compared to placebo. The Bonferroni correction was used to control for two primary group comparisons. Therefore, the original p-values were multiplied by 2 to control for type I error rate for primary efficacy test. The supportive analyses were conducted using the same approach for 6 subdomains of the FSFI. Additionally, participants were classified as either having FSD or not using an established cut-off FSFI score of 26.55. The change in

likelihood of FSD was analyzed using generalized estimation equations (GEE) approach to account for correlation between repeated assessments. Odds ratios of having FSD and 95% CI were reported as supportive evidence secondary to efficacy test on primary outcome. Moderation of baseline characteristics on the treatment effect was also evaluated in order to identify the subgroups who may benefit most from the treatment. All the supportive and exploratory analyses used $p < 0.05$ as significance level. SAS 9.4 (SAS Institute, Cary, NC) was used to perform the statistical analysis.

Results

Participant demographics for the KEEPS-sexual function ancillary study population are presented in Table 1. No significant differences were observed in baseline characteristics among the groups in parameters such as age, time from LMP to randomization, current/prior hormone use, SHBG levels, ethnicity, education, income, marital and smoking status, and severity of menopausal symptoms. There were also no significant differences at baseline between the treatment groups in the scores of the individual sexual function domains nor in the composite sexual function score, as reflected in the FSFI total score, nor in SHBG levels (Table 2). Lastly, as Table 3 demonstrates, individual domain and FSFI scores, as well as SHBG levels, were comparable at baseline across the three treatment arms and when participants were stratified by Female Sexual Dysfunction (FSD, defined as an FSFI score of less than 26.55). 72.9% of participants had FSD.

Among all participants, statistically significant improvements were observed in FSFI total score and in individual sexual function domains with o-CEE and t-E_2 treatments compared to placebo.

FSFI total score. As shown in figure 1A, the FSFI total score declined by 1.2 point (-6%) in the placebo-treated group at 48 months relative to baseline (p=0.058), with increases relative to baseline in the t-E_2-treated group at both 18 and 48 months (3.1 point or +15%, p=<0.0001 and 1.6 point or +8%, p=0.037, respectively), and in the o-CEE-treated group at 36 months (1.3 point or +9%, p=0.050). Overall, the FSFI total score significantly increased by 2.6 points (95% CI: 1.1 to 4.1, p=0.001) with t-E_2 treatment relative to placebo. The increases observed were significant at all follow-up time points (p=0.001, 0.018, and 0.005 at 18, 36, and 48 months, respectively) with consistent effect size of 2.9, 2.1 and 2.8 points respectively (p=0.63 for difference among visits), although in both the t-E_2 and placebo groups the absolute FSFI score trended downwards over time. With o-CEE treatment, the overall FSFI score increased by 1.4 points (95% CI: -0.1 to 2.8, p=0.13). However, the increase peaked at 36 months (2.3 points, 95% CI: 0.6 to 4.1, p=0.008) returning to baseline levels at 48 months (mean change from baseline: -0.3, 95% CI: -1.7 to 1.1, p=0.70). At 18 months t-E_2 group improved 2.1 points more than o-CEE group (95% CI: 0.3 to 4.0; p=0.02).

Desire and Arousal. The transdermal group showed significant increases in both desire and arousal scores at 18- and 48-months of treatment relative to baseline (p<0.0001 and p<0.03, respectively, Figure 1C, B). Significant improvements in these domains relative to both placebo and o-CEE also occurred with t-E_2 treatment at18 months (p<0.002 for desire and p<0.02 for arousal). At the 48-month time point, t-E_2 was associated with a significant improvement relative to placebo only in the arousal domain (p=0.04). No significant improvements were observed with o-CEE treatment over time.

Vaginal Lubrication and Pain. A significant decrement in lubrication score and a significant increase in pain relative to baseline was observed for participants in the placebo group at the 48 month time point ($p<0.006$, Figure 1D, F). Pain was also significantly increased at 36 months in the placebo group relative to baseline ($p=0.03$). Use of t-E_2 was associated with significant improvements relative to baseline in both lubrication and pain reduction scores at 18 months ($p<0.0008$). At this time point o-CEE was associated with significant pain reduction relative to baseline ($p=0.04$). Moreover, t-E_2 exhibited significant improvements over placebo at all time points in both lubrication and pain reduction ($p<0.01$ at 18 months, $p<0.02$ at 36 months, $p<0.003$ at 48 months). Oral CEE treatment significantly improved lubrication and pain reduction scores relative to placebo only at the 36 month time point ($p<0.03$), with a trend toward significance in the pain reduction score at 48 months ($p= 0.05$). In the o-CEE treated group, improvement in lubrication and pain reduction scores was transient, returning to baseline values at 48 months.

Orgasm. Only t-E_2 treatment significantly increased orgasm score at 18 months relative to both baseline and placebo ($p=0.002$ and $p=0.04$, respectively, Figure 1E), with a non-significant trend over placebo and o-CEE at 48 months ($p=0.056$).

Satisfaction. Sexual satisfaction scores increased in both the o-CEE and t-E_2 groups compared to baseline at 18- and 36-months of treatment ($p=0.04$ and $p=0.0002$, respectively for o-CEE; $p<0.0001$ and $p=0.01$, respectively for t-E_2, Figure 1G), with an improvement relative to baseline with t-E_2 treatment at 48 months which almost reached significance ($p=0.05$). In addition, t-E_2 significantly increased satisfaction scores relative to placebo at 18 and 36 months ($p=0.02$ and

p=0.04, respectively), whereas o-CEE significantly increased the score at only the 36 month time point (p=0.003).

SHBG levels. As SHBG levels were available only at baseline, 36 and 48 months, analysis was limited to these time points. As expected, SHBG levels were stable over time in the placebo and t-E_2-treated groups with no significant differences in the levels between the placebo and t-E_2 arms (Figure 1H). Conversely, SHBG levels significantly increased with o-CEE treatment relative to both baseline and the other treatment groups at 36 and 48 months ($p<0.0001$), although it declined significantly from 36 months to 48 months post-treatment (mean 7.5, 95% CI: 4.3 – 10.6). In a parent KEEPS study that enrolled 57 additional patients, SHBG levels were also assessed at 12 months of treatment and found to match those at 36 months.[28]

Female Sexual Dysfunction. We next analyzed the treatment effect on the risk of Female Sexual Dysfunction (FSD), defined as an FSFI score of <26.55, to determine the extent to which either treatment may have normalized sexual function, whether short term or long term. At baseline, the prevalence of FSD was 74%, 71% and 74% among o-CEE, t-E_2 and placebo groups, respectively (p=0.76). The change in proportion of participants with FSD over time in the different treatment groups is shown in Table 4, Figure 2A. As shown in Figure 2B, only t-E_2 treatment significantly reduced the odds of FSD by 36% at 18 months (OR=0.64, 95% CI: 0.42 – 0.98, p=0.04) and by 43% at 48 months (OR=0.57, 95% CI: 0.36 – 0.91, p=0.02), compared to placebo.

Because of the significant improvements in sexual function observed with t-E_2 treatment, we next performed moderation analysis to determine what factors, if any, might have influenced its

effect. After adjustment for potential confounders, age and FSD were found to affect treatment efficacy. As shown in Figure 3A, age at baseline significantly moderated the treatment effect of t-E_2 relative to placebo at 36 and 48 months. Specifically, an increase in baseline age did not significantly affect the t-E_2 associated improvement in FSFI score at 18 months (age by treatment interaction, p=0.88). However, at 36 and 48 months there was significantly less improvement observed with increasing baseline age (p=0.03), suggesting that t-E_2 may be less effective in older women. Baseline FSD status also significantly moderated the efficacy of t-E_2: We observed significant treatment effect of t-E_2 only among women with FSD at baseline, specifically at 18 and 36 months, though not among women without FSD (Figure 4A, B).

Discussion

The novelty of the KEEPS sexual function ancillary study is our ability to discern the effects of t-E_2 versus o-CEE on multiple domains of female sexual function, as well as on FSD in early postmenopausal women. Symptoms related directly to tissue effects of estrogens on the reproductive tract, such as lubrication and pain on penetration, demonstrated a progressive exacerbation with time in the untreated group, yet improved with the use of t-E_2 across all time points. In addition, the more subjective domains of desire, arousal, orgasm and sexual satisfaction demonstrated a relatively steady state over time in the untreated group, with t-E_2 imposing a consistent significant improvement in sexual function at 18 months of treatment. The contribution to the significant increase in FSFI total score in the o-CEE-treated group at 36 months appears to be predominantly due to significant improvements in the physical aspects of sexual function (lubrication and pain), though not in libido-related aspects.

The degree of improvement in FSFI that we observe with t-E_2 certainly appears to be clinically meaningful. For example, the 2.9 points improvement corresponds to about 15% improvement from baseline level, and it could reflect a change from the worst to the best in answering a single survey question, or come from one point (raw score) improvement to each of all 19 items. Temporally, t-E_2 appears to be effective earlier than o-CEE (at 18 month, 2.1 points better improvement in FSFI score), and last longer (1.8 points better at 48 month). This may be due to consistently elevated E_2 levels apparent in t-E_2 treated KEEPS participants relative to placebo and o-CEE treated women.[28] Still, the efficacy of t-E_2 treatment is limited to women with FSD, which make up the majority of healthy menopausal women with our cohort demographics (and whose frequency in the general population of postmenopausal women is in agreement with that reported previously.[29,30]) Women without preexisting FSD showed a gradual decline in sexual function after the menopause independent of treatment regimen. While women with FSD at baseline benefit from menopausal hormone therapy, those without dysfunction will not typically experience enhanced sexual function, a threshold-dependent effect that was not previously explored.

Additionally, the finding that age mediates the treatment effect of t-E_2 confirms studies demonstrating that age is a risk factor for the development of sexual dysfunction in postmenopausal women in the absence of hormone therapy.[8,31,32] Participants entering the trial at a younger age demonstrate greater improvements in sexual function with menopausal hormone therapy. Taken together, these characteristics of t-E_2 make it an attractive therapeutic agent for younger postmenopausal women with FSD.

Interestingly, confounding factors that were previously reported to affect sexual function, such as marital status,[29] smoking[33] and menopausal symptoms,[30,34] were not found to moderate the treatment effect of t-E_2. The latter factor may be due to the fact that estrogen therapy independently alleviates menopause-related symptoms, including hot flushes, night sweats, palpitations, insomnia, irritability and vaginal atrophy.[35,36] Although race, lower educational level and socioeconomic status[32,37] have also been found to adversely affect sexual function, the KEEPS population is predominantly comprised of Caucasian women of a higher educational background than the general US population, thus precluding assessment of the contribution of these factors to sexual function.

A potential mechanism accounting for the t-E_2-mediated improvement in subjective aspects of sexual function may be due to the effects of androgens and the differential ability of oral and transdermal preparations to affect SHBG. The menopause-related decline in libido has been attributed to falling testosterone[30]; therefore, SHBG-mediated reduction in bioavailable androgens could explain the lack of improvement in the desire and arousal domains observed specifically with o-CEE treatment. Indeed, a study of postmenopausal women with hypoactive sexual interest or desire associated with the onset of menopause (despite supplementation with 0.625 mg of o-CEE for 3 or more months) revealed that treatment with the combination of esterified estrogens and methyltestosterone significantly suppressed SHBG levels and increased the frequency of sexual interest or desire compared to baseline measures and relative to treatment with esterified estrogens alone[38]. However, in this study rising SHBG levels associated with o-CEE use do not appear to explain the lower efficacy of o-CEE relative to t-E_2 in improving sexual function in early postmenopausal women, as the time point associated with elevated

SHBG levels (36 months) coincides with the time point o-CEE users demonstrate the most significant improvements in the physical aspects of sexual function and in the satisfaction score.

The maximal effect of t-E_2 on subjective aspects of sexual function was seen at 18 months. At that time point the treatment effect may add or synergize with the parallel increase in serum dehydroepiandrosterone sulfate (DHEA-S), an adrenal androgen precursor whose mean circulating levels exhibited a rise in early menopause (i.e., within the 24 months after LMP) and then significantly declined two years past LMP.[39] DHEA-S was previously positively correlated with all domains of FSFI in early postmenopausal women (i.e., 1-4 year past LMP)[40] and shown to improve sexual function in supplemented postmenopausal women.[41,42] Serum DHEAS levels are not available for the KEEPS cohort, thus restricting our ability to expand further on this hypothesis, though it may be of interest to examine the effect of t-E_2 on subjective domains of sexual function beyond the 18-month point with DHEA supplementation.

Interestingly, differences in the efficacy of t-E_2 over o-CEE on sexual function were not observed in KEEPS studies investigating the effect of these treatments on postmenopausal cognitive function, mood and bone health.[43-46] Tissue-specific co-regulatory molecules that differentially recruit ERs to tissue-specific promoters, as well as tissue-specific epigenetic states of ER-responsive elements may account for this difference in treatment response. Additionally, ER-α and-β are highly expressed in the vaginal epithelium, as well as in muscle fibers and blood vessels innervating the vagina[47], making the tissue highly responsive to circulating E_2 levels. In reproductive age range bone and brain function do not fluctuate with E_2 level, however the reproductive tract is exquisitely sensitive to changes within the physiologic range of E_2; indeed

this is the basis of menstrual cycle regulation and successful reproduction. Low It is believed that basal circulating E_2 levels may be sufficient to maintain normal brain and bone function, a threshold that is provided by o-CEE. Higher circulating E_2 levels resulting from t-E_2 treatment may not differentially affect cognitive function and bone health, while the reproductive tract may be more dose responsive.

Despite the unique nature of the studied population (early menopausal women within 3 years of onset of menopause), the large sample size, the randomized controlled design of the trial and novelty of our findings, our study has some limitations that merit acknowledgement. As discussed previously, Caucasian women of educational background higher than that of the general US population characterizes the KEEPS population, thus limiting generalizability of our findings. Female sexual function is highly complex and profoundly influenced by non-hormonal factors such as culture (rev.[48]) and socioeconomic status.[49] Furthermore, information on serum levels of androgens may provide additional insights into mechanistic aspects underlying treatment-specific sexual response.

In summary, in a randomized controlled trial of hormone therapy in early postmenopausal women, both and o-CEE t-E_2 provided benefits for sexual function, but t-E_2 showed greater efficacy, especially for the subset of women with FSD. Because the efficacy declines with baseline age, early t-E_2 intervention is recommended for postmenopausal women with FSD, especially in those seeking menopausal hormone therapy for alleviation of menopausal symptoms or other health-related benefits (rev.[50]).

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