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Investigating the Effects of Estradiol or Estradiol/Progesterone Treatment on Mood, Depressive Symptoms, Menopausal Symptoms and Subjective Sleep Quality in Older Healthy Hysterectomized Women: A Questionnaire Study

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Key Words
Sex steroid treatment · Menopause · Mood · Depression · Sleep

Abstract
Clinical studies have documented that estrogen treatment often ameliorates mood disturbances and depressive symptoms occurring during the menopausal transition. The relevance of gonadal hormones for mood and well-being in healthy older nondepressed women is less well understood. Fifty-one healthy hysterectomized women (mean age 64) participated in a placebo-controlled double-blind study on the effects of gonadal hormones on cognition. They received either estradiol (2 mg estradiol valerate), estradiol plus progesterone (100 mg micronized progesterone) or placebo. Mood, well being, menopausal symptoms, depressive symptoms and subjective sleep quality were measured at baseline and after 4 and 24 weeks of treatment using three questionnaires. Thirty-five women could be included into the final analysis. Strong increases in estradiol and progesterone levels occurred in response to the treatment. The two hormones, however, had no effects on mood, well-being, menopausal symptoms, sleep quality and depressive symptoms. The current small study suggests that older healthy nondepressed hysterectomized women do not react with positive or negative mood changes to estradiol or estradiol/progesterone treatment.

Introduction

The hope to improve health and quality of life in aging with hormones (e.g. 'endocrine fountains of youth') has a long history. In fact, the usefulness, effectiveness and potential danger of hormone treatment in aging are still intensively discussed [for a recent review, see 1]. One of the most pronounced endocrine alterations in aging is the drop in gonadal steroids (estradiol and progesterone) in women after menopause. Those steroids can rapidly enter the brain and are known to influence multiple neurotransmitter systems. Estradiol modulates the serotonergic system via multiple pathways. This has been shown in rodents [2, 3], but also in experimental studies in humans using platelet markers of serotonergic activity [4] or neuroimaging techniques [5, 6]. In addition, estradiol also modulates the dopaminergic and adrenergic system [2]. Progesterone in contrast can act via its receptors, but also nongenomically by acting on the GABA receptor via its neuroactive metabolites [7, 8]. This GABA-ergic activity

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is thought to underlie the anesthetic, anxiolytic and sleep-enhancing properties of progestins [9–12].

Changes in gonadal steroids, possibly in combination with a higher sensitivity to these hormones, are thought to play a role in the mood disturbances seen in the premenstrual syndrome [13], postpartum depression [14] as well as mood disturbances associated with the menopausal transition. Indeed, hormonal interventions have been promising in these clinical syndromes [14–16].

The relevance of estrogens and progestins for mood, depression and quality of life of older healthy nondepressed women is, however, less well understood. Recent large placebo-controlled trials (HERS and WHI) using a combination of conjugated equine estrogens and medroxyprogesterone (MPA) have observed either no beneficial effect on quality of life [17] or even a decrease in quality of life in those subjects which were without menopausal symptoms at study entry [18]. In line with these negative findings of estrogens on quality of life is another recent epidemiological study [19]. However, in contrast to these findings is a large epidemiological study which observed a reduced risk for depression for women on estrogen treatment [20].

Of note is that some progestins, especially MPA have been associated with depressed mood and negative psychological symptoms in several studies [e.g. 21]. Moreover, the addition of this progestin to an estrogen treatment regime results in a blunted antidepressant effect as demonstrated in a meta-analysis [16] and in a large epidemiological study [20]. In this context, it is important to be aware of the fact that MPA differs from the naturally occurring progestin progesterone in multiple ways. For example, MPA blocks the effect of conjugated equine estrogens on tryptophan hydroxylase, the rate-limiting enzyme in serotonin metabolism. In contrast, no such effect was detectable after progesterone treatment [22].

The aim of the present small study was to assess, among other endpoints, the effects of either estradiol monotreatment or the combined estradiol/progesterone treatment on mood, depressive symptoms, menopausal symptoms and subjective sleep quality in healthy older nondepressed women.

Methods

Recruitment and Telephone Screening

Subjects were recruited through the local media for a study on 'estrogens and cognition in aging'. Several outcome measures were taken (e.g. cognitive tests and EEG measures, which will be reported elsewhere [23, 24]. The most important inclusion and exclusion criteria were screened via phone: hysterectomy; no estrogen treatment within the past 12 months; absence of cancers, tumors, deep vein thrombosis, metabolic diseases, cardiovascular diseases and neurological or psychiatric disorders. In addition, subjects had to be nonsmokers with an age between 58 and 75 years and a body mass index (kg/m^2) between 20 and 34. Lipid lowering agents, antihypertensives, aspirin, herbal products and vitamins were permitted.

Screening at University

Depression was assessed using a questionnaire (ADS-K, see below) and the presence of dementia was evaluated with the Mini-Mental State Examination (MMSE). In addition, verbal knowledge was tested as an estimate for verbal IQ. This was done using the HAWIE-R (see below) in order to balance the treatment groups with this variable on verbal intelligence. At this point, exclusion factors were a depression score in the ADS-K ≥ 21, and/or a MMSE score ≤ 23. In fact, none of the subjects had a depression score of higher than 17, the diagnostic cut off suggested by the authors of the short version of this scale [25].

Screening Instruments

Wechsler Adult Intelligence Scale – Revised. HAWIE-R, the German equivalent to the Wechsler Adult Intelligence Scale – Revised [26] is a test of verbal comprehension. It contains a list of 32 words with increasing difficulty.

Mini-Mental State Examination. MMSE is a 30-item screening test for assessment of global mental status [27]. None of the screened subjects had a low MMSE score, with the lowest score obtained being 26.

Depression Questionnaire. ADS-K, the German short version of the Center for Epidemiological Studies Depression Scale was used to measure depression (for details, see below).

Gynecological Screening

A thorough medical/gynecological checkup was performed. This entailed a medical history, a mammogram, a breast and genital tract ultrasound and a Pap-smear. Blood samples were taken and coagulation parameters were checked to assess the risk for thrombosis.

Study Design

Groups were balanced for age, BMI and verbal IQ using the minimization procedure [28] and allocated to 3 groups receiving (1) oral estradiol (2 mg estradiolvalerat, Gynokadin®, Dr. Kade, Berlin), (2) oral estradiol plus oral progesterone (100 mg progesterone, Utrogest®, Dr. Kade) and (3) oral placebo (Dr. Kade). Estradiol or placebo tablets had to be taken in the morning (around breakfast), while progesterone or placebo tablets had to be taken in the evening (before bedtime). The study design was placebo controlled and double blind. Subjects had three appointments at the laboratory: baseline, after 4 and 24 weeks. At each of the 3 appointments one blood sample was obtained for hormone analysis and subjects filled out psychological questionnaires (listed below).

The study was approved by the national ethics committee of the German Psychological Society and this vote was confirmed by the local ethics committee. All participants provided informed consent. They received financial reimbursement.

Study Participants

A total of 51 healthy elderly postmenopausal women were initially included. Nine dropped out: 3 immediately after the medical check-up because of second thoughts about the study. One woman dropped out because of painful breast tenderness in response to estradiol/progesterone treatment. Another 5 dropped out during the study because of minor health problems not typically associated with estrogen treatment (bronchitis, slight skin irritation, elevated blood pressure, gastrointestinal problems), which, however, were attributed to the hormones by the subjects. In addition, 7 subjects were excluded after the completion of data collection (5 due to noncompliance with treatment and 2 due to psychological problems occurring during the study period in response to critical life events, i.e. loss of a partner and traffic accident). Thus, 35 women could be included in the analysis reported here. The mean age was 64.1 ± 0.6 years and the mean BMI was 26.5 ± 0.6. Subjects had their hysterectomy at a mean age of 43.8 ± 1.4 years and were not treated with gonadal hormones since 13.5 ± 1.5 years.

Questionnaires

Depression Questionnaire. ADS-K is a German short version by Hautzinger and Bailer of the Center for Epidemiological Studies Depression Scale, originally developed by Radloff [29]. This questionnaire is designed for the use in general population and has been proven useful in studies with older subjects [e.g. 30, 31]. Studies conducted in Germany have shown that the scale correlates well with other depression self-rating scales like the Beck depression inventory (r = 0.78–0.84). In addition, the ADS has a sensitivity of 80–95% for depression depending on the studied population [25]. The short version contains 15 items describing specific depressive symptoms. Subjects have to rate the presence of these symptoms during the course of the last week. The response scale ranged from 0 (rarely) to 3 (most of the time) [25].

Mood Questionnaire. MDBF, long version is a German adjective checklist for the assessment of elevated vs. depressed mood, wakefulness vs. sleepiness, and calmness vs. restlessness. Each scale contains 8 items. The scale ranges from 1 (not at all) to 5 (very much) [32].

Menopausal Index. This index lists 26 symptoms categorized into 3 clusters: somatic (9 symptoms), psychosomatic (5 symptoms) and psychological (12 symptoms). The scale ranged from 0 (not present) to 4 (very strong). This questionnaire was translated and modified according to Sherwin [21].

Sleep Quality. To evaluate sleep quality, one item from the depression questionnaire (did I sleep poorly) and one item from the menopausal index (presence of sleep problems) were combined. This newly generated item ranged from 0 to 7.

Subjective Reports

At the end of the study, subjects were asked to report any physiological or psychological changes they had perceived. Out of the divergent reports only breast tenderness was reported by some subjects, and this item was coded for analysis as present versus absent.

Treatment Guess

At the end of the study, subjects were asked to guess which treatment (placebo versus hormones) they had received. This question was added in order to check whether the study maintained its double-blind design throughout the experiment.

Hormone Analysis

Serum estradiol and progesterone levels were determined using commercially available RIAs (ESTR-CTK-4 and PROG-CTK-4 from DiaSorin, Saluggia, Italy) with a sensitivity of 3 pg/ml (estradiol) and 30 pg/ml (progesterone), respectively. Inter- and intra-assay variations were below 15% for both assays.

Statistical Analysis

Effects of estradiol or estradiol/progesterone treatment on blood hormone levels as well as questionnaire results were analyzed with an analysis of variance (ANOVA) with the grouping factor treatment (placebo, estradiol, estradiol/progesterone) and the repeated measurement factor time (baseline, 4 weeks, 24 weeks).

Results

Sex Steroid Levels

Estradiol concentrations increased significantly in the estradiol group: baseline 19.4 ± 3.8 pg/ml, after 4 weeks 127.3 ± 10.7 and after 24 weeks 144.8 ± 13.3. In the estradiol plus progesterone group a similar increase occurred: baseline 23.1 ± 3.3 pg/ml, after 4 weeks 135.3 ± 14.5 and after 24 weeks 135.1 ± 16.9. No changes in estradiol levels occurred in the placebo group: baseline 23.2 ± 5.4 pg/ml, after 4 weeks 29.9 ± 5.9 and after 24 weeks 26.1 ± 3.8.

Progesterone concentrations increased significantly in the combined treatment group: baseline 0.15 ± 0.04 ng/ml, after 4 weeks 3.95 ± 0.54 and after 24 weeks 4.45 ± 0.68. In the estradiol group and in the placebo group no changes were observed. Estradiol group: baseline 0.14 ± 0.02 ng/ml, after 4 weeks 0.13 ± 0.03 and after 24 weeks 0.12 ± 0.02. Placebo group: baseline 0.20 ± 0.05 ng/ml, after 4 weeks 0.20 ± 0.04 and after 24 weeks 0.18 ± 0.04.

Table 1. Reports of breast tenderness and treatment guesses of the study participants

	PL (n = 13)		E (n = 12)		EP (n = 10)	
	yes	no	yes	no	yes	no
Breast tenderness	1	12	3	9	2	8
Hormone guess	5	7	4	8	4	6

No significant differences between the groups were observed (χ^2 analysis).

Subjective Reports

Few subjects reported subjective changes (e.g. breast tenderness) in response to the treatment, and there was no difference between the three groups ($\chi^2 = 1.40$; p = n.s.). Subjects were also unable to correctly guess which treatment they had received ($\chi^2 = 1.19$; p = n.s.). Results are presented in table 1.

Depressive Symptoms, Mood, Menopausal Symptoms and Subjective Sleep Quality

The results (mean ± SE as well as F and p values of the calculated ANOVAs) of the questionnaires are presented in table 2.

No significant effect of estradiol or estradiol/progesterone treatment was observed as indicated by nonsignifi-

Table 2. Results of the questionnaires and the corresponding ANOVAs

	PL (n = 13)	E (n = 12)	EP (n = 10)	Time by treatment interaction	Main effect time	Main effect treatment
Depression						
Baseline	8.38 ± 1.17	6.83 ± 1.41	8.50 ± 1.93	F = 0.90	F = 0.11	F = 1.18
Week 4	8.92 ± 1.61	5.75 ± 1.08	7.70 ± 1.23	p = 0.47	p = 0.89	p = 0.32
Week 24	6.85 ± 1.75	6.42 ± 1.17	9.80 ± 1.44			
Mood						
Baseline	32.23 ± 1.27	31.50 ± 1.12	33.60 ± 1.34	F = 1.58	F = 0.11	F = 1.77
Week 4	35.31 ± 1.12	31.08 ± 1.05	32.00 ± 1.44	p = 0.19	p = 0.90	p = 0.19
Week 24	34.23 ± 1.73	31.17 ± 1.20	32.80 ± 1.40			
Wakefulness						
Baseline	30.00 ± 2.04	28.75 ± 1.35	26.70 ± 2.66	F = 1.12	F = 1.47	F = 1.83
Week 4	30.38 ± 1.30	25.17 ± 1.76	25.30 ± 2.92	p = 0.35	p = 0.24	p = 0.18
Week 24	30.77 ± 1.65	27.50 ± 1.86	24.90 ± 2.73			
Calmness						
Baseline	27.08 ± 1.50	27.83 ± 1.90	28.90 ± 2.31	F = 1.03	F = 2.28	F = 0.03
Week 4	29.31 ± 1.71	27.92 ± 1.76	29.00 ± 1.62	p = 0.40	p = 0.11	p = 0.97
Week 24	29.62 ± 1.58	29.42 ± 1.69	28.90 ± 1.56			
Menopause Index (total)						
Baseline	25.54 ± 2.59	19.75 ± 4.22	23.60 ± 4.94	F = 0.07	**F = 6.20**	F = 0.82
Week 4	21.62 ± 3.33	16.42 ± 2.55	20.10 ± 3.48	p = 0.97	**p = 0.01**	p = 0.45
Week 24	19.85 ± 4.01	15.08 ± 2.25	17.10 ± 2.63			
Somatic complaints						
Baseline	7.69 ± 0.79	6.92 ± 1.95	6.30 ± 1.63	F = 0.17	F = 1.57	F = 0.82
Week 4	7.15 ± 0.99	6.42 ± 1.36	5.10 ± 1.24	p = 0.91	p = 0.22	p = 0.45
Week 24	7.08 ± 1.85	5.25 ± 0.58	4.50 ± 0.86			
Psychosomatic complaints						
Baseline	3.77 ± 0.61	2.25 ± 0.84	2.30 ± 1.01	F = 0.54	F = 2.58	F = 1.12
Week 4	3.62 ± 0.92	2.08 ± 0.58	2.70 ± 1.23	p = 0.69	p = 0.09	p = 0.34
Week 24	2.23 ± 0.67	1.25 ± 0.45	2.30 ± 0.72			
Psychological complaints						
Baseline	14.08 ± 1.62	10.58 ± 2.04	15.00 ± 2.64	F = 0.41	**F = 6.93**	F = 1.11
Week 4	10.85 ± 2.32	7.92 ± 1.10	12.30 ± 2.16	p = 0.79	**p < 0.01**	p = 0.34
Week 24	10.54 ± 2.27	8.58 ± 1.73	10.30 ± 1.78			
Sleep quality						
Baseline	3.46 ± 0.43	2.92 ± 0.56	2.50 ± 0.52	F = 0.54	**F = 9.12**	F = 0.49
Week 4	2.54 ± 0.40	1.92 ± 0.47	2.20 ± 0.51	p = 0.70	**p < 0.01**	p = 0.62
Week 24	2.15 ± 0.42	1.83 ± 0.52	1.90 ± 0.62			

F and p values are from a treatment (PL, E, EP) by time (baseline, 4 weeks, 24 weeks) ANOVA. Significant F and p values are printed in **bold**.

cant ($p > 0.20$) group by time interaction for all three questionnaires as well as for the sleep variable. A significant main effect time was detected for the total score in the menopause index, in the subscale psychological symptoms in the menopause index and for the sleep variable, indicating that over the course of the study subjects reported less psychological symptoms and increased sleep quality irrespective of the treatment they had received.

Discussion

The current small study found no evidence for a strong effect of estradiol or estradiol/progesterone treatment on mood, depressive symptoms, menopausal symptoms and subjective sleep quality in older healthy nondepressed hysterectomized women. Neither significant positive effects of estradiol monotreatment nor significant negative effects of the combined treatment could be detected. Participating women reported few negative side effects and these side effects did not differ between the two active treatment groups and the placebo group. Consequently, the subjects were unable to correctly guess whether or not they had received hormones. Therefore, the study successfully maintained a double-blind nature, which is in contrast to studies in young women or studies in women with intact uteri.

For several of the obtained psychological measures, significant longitudinal effects irrespective of the treatment were observed. These can be interpreted as placebo effects [33] and/or as the beneficial effect of study participation. The longitudinal changes demonstrate that the used questionnaires were sensitive enough to pick up changes induced by study participation and argue against a ceiling effect for mood in this healthy nondepressed sample.

The small size of the current study certainly raises issues of statistical power. However, at least in younger women effects of gonadal hormones on mood were detected with similarly small study groups [e.g. 21, 34]. Nevertheless, the current study certainly would have been unable to detect small effects, even though those might not be of clinical interest.

We studied a healthy older nondepressed population, and therefore results can not be extrapolated to effects possibly obtained in psychiatric patients (e.g. subjects with clinically manifested depression). One weakness of our study is the absence of a thorough psychiatric screening at baseline, which was not feasible in the context of this study. Moreover, the current results solely rely on questionnaire data; thus, we cannot exclude the possibility that other psychiatric measures (e.g. ratings of trained psychiatrists) would have detected effects of the treatment.

Basic neuroscience studies have observed several effects of estradiol on the CNS with possible relevance for mood, most notably estradiol can modulate the serotonergic system [2]. Several studies have observed beneficial effects of estradiol on mood or depression in women with either menopausal symptoms [e.g. 18, 34] or depression [16]. Still, negative results have also recently been reported in older depressed women [35]. Studies with healthy nonsymptomatic women have been less convincing. The nonsignificant findings obtained in the current study are in agreement with several large-scale studies demonstrating no favorable effects of hormone treatment on quality of life or mood in healthy older women [17, 18]. Similar nonsignificant findings have been reported for the adrenal sex hormone precursor dehydroepiandrosterone [36–38]. Together, these studies might suggest that mood and well-being of healthy older women does not benefit from sex steroid treatment. This would be in contrast to the claims from some of the supporters of 'anti-aging medicine' [1, 39] who at times strongly support sex hormone treatment or 'replacement' for healthy nonsymptomatic older women and men.

In addition to the absence of beneficial effects of estradiol, we also did not observe any evidence for mood impairing effects of progesterone, which is in contrast to some previous studies [16, 18, 21]. For example, using the same menopausal symptoms questionnaire, Sherwin observed an increase in psychological symptomatology in younger menopausal women (age 47–57 years) in response to treatment with the progestin MPA [21]. Future studies are needed to determine whether the age and baseline characteristics of the subject (e.g. presence of mood disorders and/or menopausal symptoms) or the used progestin (MPA versus the naturally occurring progesterone [40]) is responsible for these results.

Neither estradiol nor estradiol/progesterone treatment had any effects on subjectively reported sleep quality, which was crudely assessed with two items taken from the depression and the menopausal symptom questionnaire. The importance of gonadal hormones for sleep in older women is still incompletely understood. Several previous sleep EEG studies resulted in conflicting results probably reflecting differences in studied subjects and used hormonal treatments [e.g. 41–43]. Several possible direct or indirect mechanisms of action of estrogens or progestins have been discussed in this context [for reviews, see 11,

44]. Previous basic science studies in animals as well as young healthy men (used dose: 300 mg) had shown that progesterone administration resulted in effects similar to those induced with GABA agonists [45, 46]. Our study at least suggests that progesterone taken in the evening has no strong effects on subjective sleep quality in healthy older women. Results might have been different if subjects were included into the study based on sleep disturbances [47]. Ideally, such future studies would combine objective (sleep EEG) measures with more elaborated questionnaires like the Pittsburgh Sleep Quality Index [48].

In sum, the present small study failed to find any effects of estradiol or progesterone treatment on mood, depressive symptoms, menopausal symptoms or subjective sleep quality in healthy older women when given acutely (4 weeks) or during a more prolonged (24 weeks) period. Whether these findings in turn also suggest that terminating estrogen or estrogen/progesterone treatment in this age range (as suggested by some as a result of the WHI findings [49]) would have no negative effects on mood and quality of life awaits to be determined using an experimental approach [50].

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