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Comparison of low dose versus ultra-low dose hormone therapy in menopausal symptoms and quality of life in perimenopause women

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ABSTRACT

The study was to compare the efficacy, safety, and tolerability of low dose versus ultra-low dose hormone therapy (HT) in the management of perimenopause symptoms and quality of life. Retrospective analysis of perimenopause patients prescribed for 25 weeks HT in the outpatient clinic of menopause. A total of 132 perimenopause women were included in two treatment regimens: one with low dose HT (LD-HT) and one with ultra-low dose HT (ULD-HT). Changes in serum levels of follicle-stimulating hormone, estradiol as well as transvaginal ultrasound (TVUS), the 36-item Short Form Health Survey (SF-36), the Kupperman Index (KI), and adverse effects were assessed at baseline, 4, 13, and 25 weeks. By the end of 25 weeks of treatment, each score of SF-36 domains for both LD-HT and ULD-HT groups were increased, the KI decreased, and the endometrial thickness increased in both groups and there was no statistical difference between two groups. Both groups have negligible differences in incidence of adverse effects. Low dose and ultra-low dose HT both can serve in improving symptoms of perimenopause, thereby offering a better quality of life with decreased incidence of side effects. Ultra-low dose treatment may have a better advantage on safety and tolerance.

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Introduction

During the menopause transition, women often suffer from a variety of symptoms that may exert negative impact on their daily activities, physical and mental health, and quality of life [1]. Menopause symptoms are one of the chief complaints for which women worldwide seek medical treatment. Hormone therapy (HT) has proved to improve the number and severity of menopause symptoms, thereby enhancing the general quality of life [2–4].

The fundamental essence of HT is estradiol. Standard therapeutic doses include 0.625 mg conjugated equine estrogen and a comparable dose of other estrogen [5], such as 2.0 mg 17 β -estradiol, 2.0 mg estradiol valerate, 50 μ g transdermal estradiol, and 2.5 mg tibolone. The minimum effective dose of HT has been proposed. Nowadays, there are many studies being conducted to investigate on the relatively low doses of HT [6], but most of them are based on postmenopausal women rather than perimenopause women. According to the current guidelines for the management of climacteric symptoms, the lowest effective dose of estradiol should be used and each patient should have a tailored regimen of HT to better enhance the beneficial effects while minimizing the relative risks associated to it [7]. Many research studies have also demonstrated that relatively low doses of HT gave the same positive effects as standard dose therapy in alleviating menopausal symptoms, hot flushes, vaginal atrophy and in preventing osteoporosis [8–12]. Some other studies on lower dose of HT showed that many harmful effects and potential risks could be decreased [13].

Chinese women, as with the perimenopause women in many countries, are quite worried about the risks of this medical intervention with choosing it hesitatingly [14,15]. We conducted this study aiming to assess the efficacy of an oral low and ultra-low dose regimen in treating climacteric symptoms and improving quality of life in perimenopause women. To help patients better direct the lowest effective dose complying with the current guidelines, alongside to avoid the adverse effects and potential risks of HT.

Methods

Study design and participants

Database was set up for patients with HT during June 2015 to June 2017 on menopause clinic in Women's Hospital, Zhejiang University, School of Medicine. Baseline information, medical regimen, and follow-up records were collected and preserved in computer software. A total of 363 cases were registered, from which we selected 132 perimenopause women, aged 38–55 years, cessation of menses for 0–12 months, a serum follicle-stimulating hormone (FSH) levels > 25 IU/L, a Kupperman index (KI) \geq 10 [16], continued receive for 25 weeks HT treatment. Two regimens were included: 63 women were given a low dose combined HT (LD-HT) containing estradiol valerate (Progynova, Bayer, France), 1 mg daily with dydrogesterone (Duphaston, Abbott, Netherland), 10 mg daily for 14 days from the 12th day of menstrual cycle or 30th day since last beginning dydrogesterone time

with amenorrhea for protection of endometrium, and 69 women received an ultra-low dose combined HT (ULD-HT) containing 0.5 mg of estradiol valerate daily with the same dose dydrogesterone. All participants committed to oral drugs at a regular time per day.

The local ethical committee approved this study and an informed consent was obtained from each subject.

Assessments

Age, height, weight, body mass index (BMI), and the time of amenorrhea were recorded before the treatment. Furthermore, visits for reassessment were scheduled at 4, 13, 25 weeks after treatment initiation.

The participants completed the SF-36 scale [17,18], which to measure the health quality of life, and the KI scales, which to evaluate the menopause syndrome. TVUS was performed before and after the treatment at the 9th day of the menstrual cycle or progesterone withdraw period when coming with amenorrhea. Laboratory parameters (the levels of FSH and estradiol hematologic routine clinical biochemistry) were measured.

Statistical analysis

SPSS19.0 statistical software was adopted to conduct descriptive statistics of the data. The Kolmogorov–Smirnov test was used to identify whether the sample came from a population that was normally distributed. For normal distributed data, the paired *t*-test was used to compare values within groups, the independent *t*-test was used to compare means from independent groups. Categorical variables were compared using Chi-square test and Fisher's exact test. The Mann–Whitney *U* test and Wilcoxon signed-rank test for non-parametric variables were executed. Data are presented as the mean ± standard deviation (SD) or mean ± standard error (SE). All *p* values < .05 were considered to be statistically significant.

Results

Among all 132 participants, the average age was 46.21 years, suffering an average amenorrhea time was 4.68 months. The baseline demographic characteristics of the women in the two treatment groups were comparable, as shown in Table 1. There was no significant difference between age, duration of amenorrhea, weight, BMI, the levels of serum FSH of the two groups at the baseline (*p* > .05). The levels of serum estradiol between the

two groups were showed a statistic difference (*p* < .05), but all in a quite low level without clinical difference.

After 25 weeks HT treatment, the serum FSH decreased in both LD-HT and ULD-HT groups comparing with the baseline (both *p* < .05), and no difference at week 25 between the two groups (*p* > .05) were noted. Both groups showed a significant increase in plasma levels of estradiol (both *p* < .05) and no difference was noted at week 25 between them (*p* > .05). Weight gain is a common complaint in menopausal women while undergoing HT [19]. In this study, we found that there was no statistic change in weight after treatment in both groups (*p* > .05). The BMI remained unchanged after treatment in both group (*p* > .05).

The data of the scores in each SF-36 domain for the overall sample as shown in Figure 1(A–I). The mean scores of the SF-36 domains at baseline were similar in both groups (*p* > .05). As compared to baseline values, the quality of life of subjects at week 25 was improved considerably. The improvement of role physical, body pain, general health, vitality, role emotional, and health transition was statistically significant in both groups (*p* < .05). Other domains, including physical functioning, social functioning, and mental health, showed a certain amount of improvement, though there was no statistical difference (*p* > .05). There was no statistical significance between the two groups in all domains after treatment (*p* > .05).

The baseline scores of the KI were similar in both LD-HT and ULD-HT (17.53 ± 6.24 and 17.38 ± 10.72, respectively, *p* > .05) groups. The KI showed a reduction during treatment in the two groups along 25 weeks. There was a statistically significant difference on the reduction of the index in both groups compared to baseline at each assessment after treatment (*p* < .01 for all). No statistical difference was found between the two groups at weeks 4, 13, and 25 (*p* > .05) (Figure 1(J)).

Mastodynia was the primary complaint of HT users [2]. The incidence was 36.51% (23/63) in the LD-HT group and 20.29% (14/69) in the ULD-HT group showing the LD-HT group had a higher occurrence rate (*p* < .05) in this study. Abnormal uterine bleeding (AUB) caused by ovulatory dysfunction is common in perimenopause women. Majority of the subjects however did not experience AUB during HT treatment period. Outcomes being, only 3 (2.27%) patients came up with AUB in this study, 2 (3.17%) in the LD-HT group and 1 (1.45%) in the ULD-HT group (Table 2). The uterine endometrial thickness increased in both groups after treatment, LD-HT groups showed a significant growth (*p* < .05), while there was no statistically significant difference between the two groups.

Table 1. Characteristics of the participants and changes in serum index.

Characteristics	All (<i>n</i> = 132)	LD-HT group (<i>n</i> = 63)	ULD-HT group (<i>n</i> = 69)	<i>p</i> ^a
Age (years)	46.21 ± 4.02	45.72 ± 4.17	46.29 ± 4.09	NS
Duration of amenorrhea (months)	4.68 ± 3.53	4.20 ± 3.39	5.03 ± 3.35	NS
Weight at baseline (kg)	55.47 ± 6.76	55.34 ± 5.67	56.20 ± 6.88	NS
Weight at 25th week (kg)	55.56 ± 6.39	55.26 ± 5.74	55.71 ± 6.80	NS
BMI at baseline (kg/m ²)	21.83 ± 2.33	21.80 ± 2.19	21.82 ± 2.28	NS
BMI at 25th week (kg/m ²)	21.72 ± 2.25	21.70 ± 2.29	21.38 ± 2.20	NS
FSH at baseline (IU/L)	74.33 ± 27.27	71.08 ± 27.89	76.98 ± 26.57	NS
FSH at 25th week (IU/L)	47.32 ± 26.31	42.08 ± 20.59 ^b	51.41 ± 29.37 ^b	NS
Estradiol at baseline (pmol/L)	92.70 ± 124.73	124.50 ± 161.67	68.28 ± 120.79	<0.05
Estradiol at 25th week (pmol/L)	269.79 ± 251.73	273.56 ± 202.31 ^b	264.48 ± 287.07 ^b	NS

Data are presented as mean ± standard deviation (SD). BMI: body mass index; FSH: follicle-stimulating hormone; NS: no statistical significance.

^aComparison between LD-HT and ULD-HT groups.

^bIndicates that the treatment changes compared with baseline was statistically significant (*p* < .05).

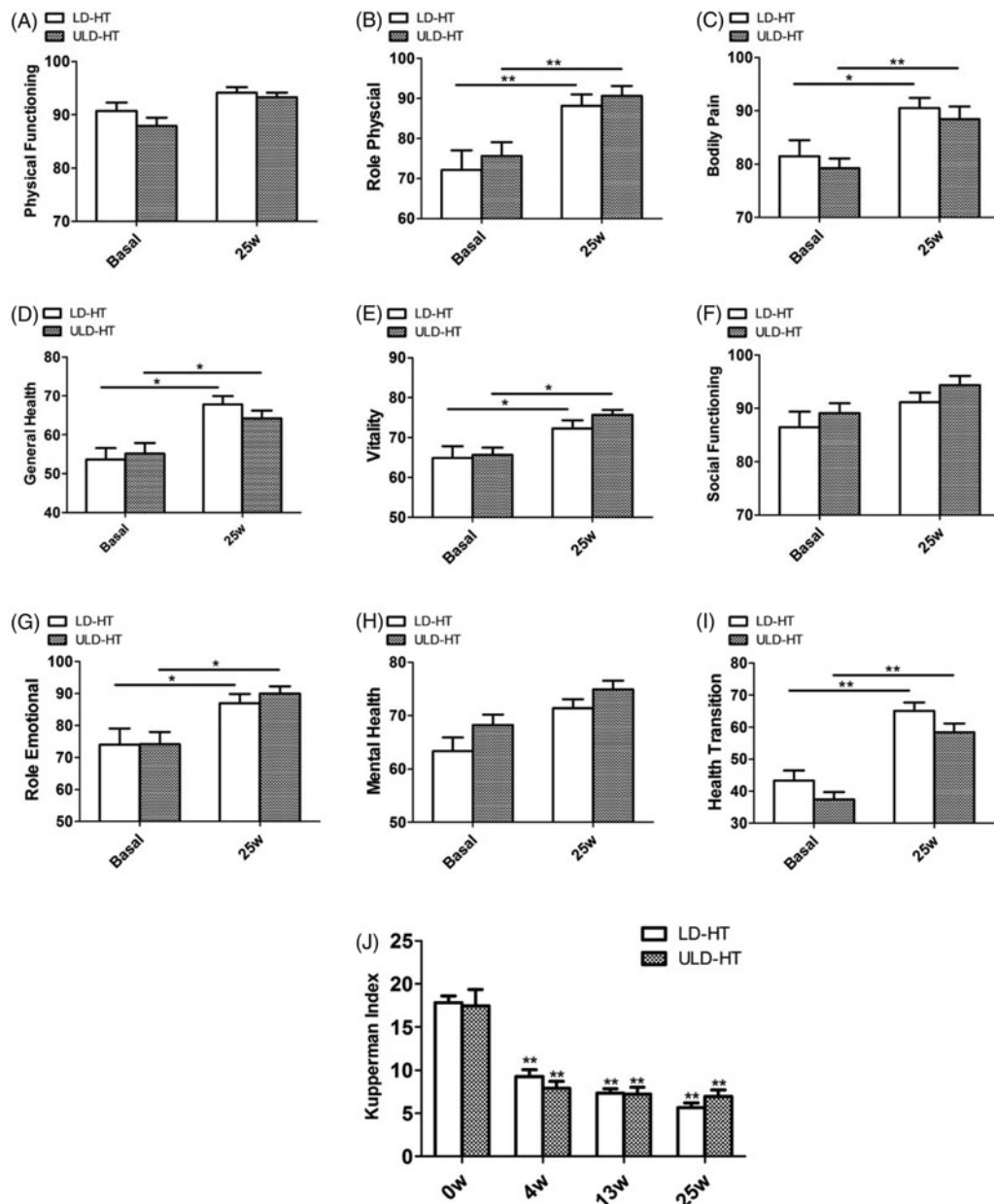


Figure 1. (A–I) Nine domains of SF-36 index before and after HT treatment. (J) Kupperman index noted at baseline and after 4, 13, and 25 weeks treatment. All data are presented as mean \pm standard error (SE). p values for comparisons between baseline and post-treatment. * $p < .05$. ** $p < .01$.

Table 2. Incidence of adverse events and increasing of endometrial thickness.

Variables	All (n = 132)	LD-HT (n = 63)	ULD-HT (n = 69)	p^a
Mastodynia	37 (28.03%)	23 (36.51%)	14 (20.29%)	<.05
Abnormal uterine bleeding	3 (2.27%)	2 (3.17%)	1 (1.45%)	NS
Endometrial thickness at baseline (mm)	1.98 \pm 0.85	1.98 \pm 0.83	1.97 \pm 0.88	NS
Endometrial thickness at 25th week (mm)	2.17 \pm 0.96	2.32 \pm 0.12 ^b	2.07 \pm 0.78	NS

Values of adverse events are presented as n (%). Values of endometrial thickness are presented as the mean \pm standard deviation (SD). NS: no statistical significance.

^aComparison between LD-HT and ULD-HT groups.

^bIndicates that the treatment change compared with baseline was statistically significant ($p < .05$).

Discussion

HT is used worldwide for relieving the menopause symptoms. This study sought to obtain data on the association and preliminary efficacy of low dose and ultra-low dose HT for reducing perimenopause symptoms and proving quality of life.

This study was carried out in two groups of perimenopause women with similar age, duration of amenorrhea, weight, and BMI, as well as the serum levels of FSH and estradiol at baseline. The mean age of the whole group was 46.21 years, which was rather younger than the average menopause age [20]. From that,

women suffering the menopausal symptoms for a long time since perimenopause period with irregular cycles, and maybe that's why they were seeking for medical intervention. Endocrine hormones were fluctuated drastically during perimenopause period, but in our study, it seems stable in FSH and estradiol during HT time. After 25 weeks HT treatment, the serum levels of FSH decreased in both LD-HT and ULD-HT group, the estradiol increased, and no significant difference between the low and ultra-low dose treatment group.

The SF-36 and KI are used worldwide and conformed to the requirements of quality of life and climacteric symptoms. Previous studies have demonstrated that the beneficial effects of estradiol are dose dependent [21]. In the study of Polisseni et al. [22], postmenopausal women used in low dose HT treatment (1 mg estradiol + 0.5 mg norethindrone acetate, E2/NETA, $n = 56$) for 12 weeks showed an improvement in quality of life (77.73 ± 15.3 versus 55.7 ± 16.7 , $p < .05$) by using the Women's Health Questionnaire (WHQ). According to other authors, same conclusion had been come out [23]. Now, the impact of HT treatment on quality of life in the postmenopausal women remains consistent, but few studies have been implemented on perimenopause women. Yu et al. [21] and Min [24] have proved that low dose HT lead to a positive effect in the reduction of KI scores in perimenopause women. Comparable effects of low dose HT and ultra-low dose HT were demonstrated in our study on both SF-36 and KI scores. In our previous study [25] that surveyed the quality of life and its associated factors used SF-36, Chinese women might have a decline in quality of life mainly in physical health while remaining stable in mental health, as differences were seen in physical functioning, role physical, and bodily pain but not in vitality, role emotional, and mental health by menopausal stages. In this study, all domains of SF-36 manifested an improvement in both treatment groups were observed, especially in the domains of role physical, bodily pain, general health, vitality, role emotional, and health transition. There was no significant difference between the two observed groups after treatment in all domains, which is consistent with previous studies in postmenopausal women. The KI scores reduced drastically compared with the basic level throughout the treatment in both groups, which are consistent with previous studies. The obvious changes started at week 4 of treatment and no significant difference between the two groups was observed ($p < .01$ for each assessment compared to baseline and $p > .05$ for comparison between two groups).

A low frequency of adverse effects is shown in lower dose HT [26]. In a review by Peeyanjarassri and Baber [6], it was analyzed that many studies showed a dose-related effect on per breast tenderness and vaginal bleeding with estrogens. In our study, the incidence of mastodynia seems at a low level (36.51 and 20.29% respectively), especially in ULD-HT group. During the first 3 months of continuous combined treatment, 63–80% of low-dose HT users reported no bleeding, increasing to 82–97% after 12 months [6]. In our study, majority of the subjects did not experience bleeding in both groups. Less happening of mastodynia and AUB will be much more welcome in women who were afraid of the side-effects. As a result, endometrial thickness increases in both groups after HT in our research, however, that in patients treated with ULD-HT was not statistically significant. This indicated that a much lower dose treatment had less influence on endometrial hyperplasia, it seems much safer in cancer risk.

This study has several limitations. First, the sample size was too small. Second, this study did not collect a placebo group or a

standard therapeutic dose treatment group to compare the measurement before and after the treatment, which can only evaluate associations between dose and the outcomes. Third, residual confounding is still possible. Variables that were not contained in this study may give rise to confounding in the results. Factors including lifestyle, education, chronic disease, anxiety, and depression, which were found to associate with self-perceived menopausal symptoms and quality of life [15,27].

Conclusions

In conclusion, oral low and ultra-low doses of continuous sequential 0.5 and 1 mg estradiol valerate, with 10 mg dydrogesterone were effective in alleviating perimenopause symptoms and improving quality of life in perimenopause women, and no significant difference were found. Both were associated with a low incidence of adverse events and a good tolerability profile, but ultra-low dose treatment may have a better advantage on safety and tolerance.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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