Analysis of the long-term beneficial effects of menopausal hormone therapy on sleep quality and menopausal symptoms

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Abstract. A large number of menopausal women report sleep disturbances along with psychological, somatic and urogenital menopausal symptoms. The aim of this study was to evaluate the efficacy of menopausal hormonal therapy (MHT) in improving subjective sleep quality and the severity of menopausal symptoms. An institutional ethics committee approved this retrospective chart review of 342 women treated with MHT for menopausal symptoms. Standard 28-day MHT consisted of the oral administration of 2 mg estradiol daily for 14 days, followed by 2 mg estradiol and 10 mg dydrogesterone daily for the remaining 14 days. A subgroup of 14 participants with a family history of cancer and mammography scores of 3 and above, received only tibolone 2.5 mg daily. Perceived sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI), while the assessment of menopausal symptoms was performed using the Kupperman Menopause Index (KMI) and menopause rating scale (MRS). Of the 342 patients, 79 were followed-up for 3 years. Compared to the baseline scores, the mean decrease in PSQI scores was 1.53±0.29 points (P<0.0001) at 1 month, 2.21±0.187 points (P<0.0001) at 2 months and 2.26±0.6 points (P<0.0001) after 3 years of MHT. The KMI scores also decreased by a mean of 6.37±1.59 points (P<0.0001) at 1 month and by 8.73±1.92 points after 3 years (P<0.0001). The MRS scores decreased by a mean of 3.56±1.05 points (P<0.0001) at 1 month and by 4.28±2.01 points (P<0.0001) after 3 years, as compared to the baseline scores. Patients receiving tibolone MHT did not report any improvement in sleep quality (P=0.956). On the whole, the findings of this study indicate that conventional MHT has a rapid and prolonged beneficial effect on self-reported sleep quality and menopausal symptoms in women. However, further clinical studies are warranted to compare the effects of different MHT regimens.

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Introduction

Menopause is defined as the end of a woman's reproductive period, associated with the decreased production of estradiol and progesterone by the ovaries (1). With increased life expectancies worldwide, it is estimated that by 2025, the number of post-menopausal women will reach 1.1 billion (2). The gradual or sudden cessation of ovarian follicular function can manifest in a number of psychological, somatic and urogenital menopause symptoms that have a significant impact on the quality of life of women (3). These severity of climacteric complaints is routinely determined by using the Kupperman Menopause Index (KMI) and the menopause rating scale (MRS) (4,5) that evaluate menopause-related somato-vegetative, psychological and urogenital symptoms (6).

Insomnia is considered one of the most common symptoms of menopause, occurring in over half of climacteric women (7-11). Chronic poor sleep has the most profound negative effect on the quality of life of menopausal women (12-14), and can also lead to the development and exacerbation of cardiovascular and metabolic diseases (15). Therefore, addressing emerging sleep symptoms during menopause may significantly improve the overall health and wellbeing of women.

Systemic estrogen/progestin menopausal hormone therapy (MHT) is one of the most common treatments used to counteract menopausal symptoms, such as hot flashes, night sweats and urogenital atrophy (16). However, in women with a previous history of breast cancer, conventional estrogen/progestin MHT may increase the risk of recurrence. This risk may be reduced by the use of progestogens, and among these, is the synthetic steroid tibolone, whose metabolites have estrogenic, progestogenic and androgenic properties (17). The effect of MHT on sleep quality remains poorly understood. Several randomized clinical trials have demonstrated that estrogen/progestin MHT results in slightly improved sleep quality in menopausal women with vasomotor symptoms (18,19). However, significant heterogeneity in the selection criteria of the trial participants and formulations of MHT make it is difficult to determine whether the same effect could be achieved in general population of menopausal women (19).

Sleep disturbances can be either evaluated by objective methods such as polysomnography, or by using patient-filled questionnaires, such as the self-rated Pittsburgh Sleep Quality Index (PSQI) that assesses sleep quality and disturbances over a time interval (20,21). A systematic review by Devine *et al* demonstrated that questionnaires filled by the patient are an accurate tool for predicting the quality of sleep, and evaluating the efficacy of different treatments (22).

In this study we use PSQI to assess the effects of estrogen/progestin and progestogen MHT on sleep quality, and further examined the effects of MHT on the overall quality of life of women experiencing menopausal symptoms.

Subjects and methods

Study design and participants. The Ethics Committee of the Maternity and Child Health Care of Zaozhuang approved this retrospective medical record review (approval no. 2016006). From the history reports of the patients who were enrolled in this study, all patients or patient carers signed informed consents. A total of 342 women newly attending the outpatient clinic who were naïve to MHT treatment were enrolled in this study. The menopausal status of the participants was assessed by their self-reported menstrual history. Menopause was determined as the cessation of menstruation with 12 months of amenorrhea. All participants were required to fill in a demographic form, as well as detailed medical history, including the characteristics of menopause, urogenital and metabolic disorders, and any previous history of oncological diseases. The study was approved by the ethics review board of the hospital and each participant provided their written informed consent prior to participation.

MHT. All participants enrolled in this study received MHT. Women with no family history of breast cancer and mammography scores <3 received femoston (estradiol/dydrogesterone 2/10 mg, Abbott laboratories) according to the established standard protocol. Briefly, 1 red tablet, containing 2 mg estradiol was administered daily for the first 14 days, and 1 yellow tablet, containing 2 mg estradiol and 10 mg dydrogesterone was administered daily for the following 14 days of each 28-day cycle orally. A subgroup of 14 participants with a family history of cancer and mammography scores ≥3, received tibolone (Livial®; Organon), 2.5 mg daily.

Determination of sleep quality and severity of menopausal symptoms. Perceived sleep quality was measured and scored with the PSQI, as previously described (23). A total score >5 indicates insufficient sleep quality; a PSQI ≤5 indicates good sleepers, while a PSQI >5 corresponds to poor sleepers. The assessment of menopausal symptoms was performed using the KMI and the MRS that measure the severity of age-/menopause-related complaints by rating a profile of symptoms and their impact on health-related quality of life.

Statistical analysis. All variables are expressed as the means ± standard deviation. Follow-up data at each time interval was compared using a one-way analysis of variance test (ANOVA) followed by Tukey's honestly significant difference (HSD) test. Values of $P<0.05$ were considered to indicate statistically significant differences.

Results

This study comprised of 342 women with an average age (SD) of 50.3 (5.6) years. The baseline demographic and medical characteristics for all the subjects are summarized in Table I. The mean weight of the participants was 56.5 (7.3) kg and the average age at the onset of menses was 14.3 (1.6) years. The majority of women enrolled in this study (95.9%) had no family history of breast disease. In addition, the majority of women did not suffer from or were treated for cervical, endometrial or ovarian cancer prior to exhibiting menopausal symptoms (100, 99.7 and 100%, respectively). The majority of women did not have a confirmed diagnosis of endometriosis and uterine fibroids (99.4 and 95.9% respectively), and had not undergone any type of urogenital surgical interventions (98.8%). The majority of participants also had no previous history of hypertension (93.9%), diabetes (98.8%), lipid metabolism disorders (94.2%), gallbladder disease (94.4%) or thyroid dysfunction (90.6%).

At the start of the study (baseline), the mean PSQI score of the participants was 9.16 (4.84) points, indicative of a poor sleep quality (Table II). At 1 month after the commencement of beginning MHT, the participants reported significantly improved sleep quality as indicated by the reduction in the PSQI global sleep quality score (decrease of 1.53 points; $P<0.0001$), as compared to the baseline score. The PSQI score further decreased at 2 months after the commencement of MHT (2.21 points, $P<0.0001$), and continued to remain significantly below baseline scores throughout the 3 years of continuous treatment ($P<0.0001$). After 3 years of MHT, the participants continued to maintain a mean decrease (SD) of 2.19 (0.21) points (1.3-fold) as compared to the baseline score (Fig. 1).

The mean (SD) KMI score of the participants at the baseline was 18.63 (9.86) (Table III). We observed a 6.37 (1.59) point decrease in the score during the 1st month of MHT ($P<0.0001$). The KMI scores continued to gradually decline throughout the course of hormone therapy, reaching an average of 9.9 (7.33), with a decrease of 8.73 (1.92) points compared to the baseline score ($P<0.0001$; Fig. 2).

There was a significant [3.56 (1.05) points ($P<0.0001$)] decrease in the mean MRS scores of the participants during the 1st month of MHT as compared to baseline (Fig. 3). Subsequent hormone treatment did not result in further significant changes in the MRS scores (Fig. 3), and the average score at 3 years after the commencement of MHT was 4.7 (4.6), as compared to 8.66 (6.17) at baseline, an equivalent of 3.96 (2.01)-point decrease ($P<0.0001$; Table IV and Fig. 3).

We then evaluated whether different MHT regimens (femoston or tibolone) had a different impact on the changes in the PSQI scores. In the subgroup of participants receiving femoston, the baseline mean PSQI score was 9.14 (4.84) points (Table V). During the 1st and 2nd months of MHT, the PSQI score improved significantly, exhibiting a decrease of 1.62 (1.01) ($P=0.04$), and 2.26 (0.72) points ($P=0.0002$) respectively, comparing to baseline (Fig. 4). There was no further significant decrease in the PSQI score, maintaining a stable

Table I. Demographic characteristics and medical history of the participants.

Demographics	No. of participants	Mean	(±SD)
Age	342	50.3	5.6
Weight (kg)	325	56.5	7.3
Age at 1st period	181	14.3	1.6
Medical history	**No. of participants**	**Yes (%)**	**No (%)**
Dysmenorrhea	182	66 (36.8)	115 (63.2)
Stress before period	182	33 (18.1)	149 (81.9)
Gynecological surgery	342	54 (15.8)	288 (84.2)
Family history of breast disease	342	14 (4.1)	328 (95.9)
History of endometrial cancer prior to onset of menopausal symptoms	342	0 (0.0)	342 (100.0)
Treated for cervical cancer prior to onset of menopausal symptoms	342	1 (0.3)	341 (99.7)
History of ovarian cancer prior to onset of menopausal symptoms	342	0 (0.0)	342 (100.0)
Confirmed diagnosis of endometriosis	342	2 (0.6)	340 (99.4)
Surgical interventions for uterine fibroids	342	14 (4.1)	328 (95.9)
Gynecological benign surgery - other surgeries	342	4 (1.2)	338 (98.8)
Tumor (current)	342	0 (0.0)	342 (100.0)
History of hypertension	342	21 (6.1)	321 (93.9)
History of diabetes	342	4 (1.2)	338 (98.8)
History of lipid metabolism disorder	342	20 (5.8)	322 (94.2)
History of gallbladder disease	342	19 (5.6)	323 (94.4)
History of thyroid disease	342	32 (9.4)	310 (90.6)
History of other diseases	342	20 (5.8)	322 (94.2)

Variables with a number <342 indicate missing collected data from some of the subjects. Numbers in parentheses are in percentages.

Table II. Comparison of PSQI scores of the study participants at baseline and follow-up assessments.

MHT period	No. of participants	PSQI mean (±SD)	Delta-PSQI mean (±SD)	One-way ANOVA (P-value)	Tukey's HSD post-hoc test[a] (P-value)
0 days (baseline)	342	9.16 (4.84)	0	N/A	-
1st month	111	7.63 (4.58)	1.53 (0.29)		-
2nd month	108	6.97 (4.50)	2.21 (0.187)		<0.0001
3rd month	93	7.02 (4.01)	2.16 (0.2)		<0.0001
>3 months	171	6.95 (4.32)	2.21 (0.221)		<0.0001
>6 months	113	6.97 (4.33)	2.19 (0.191)	<0.0001	<0.0001
>9 months	84	7.37 (4.41)	1.79 (0.139)		<0.0001
>1 year	134	6.90 (4.17)	2.28 (0.19)		<0.0001
>2 years	76	6.71 (4.56)	2.45 (0.161)		<0.0001
>3 years	79	6.90 (4.76)	2.26 (0.6)		<0.0001

All 342 subjects received hormone treatment. The PSQI scores were recorded prior to the commencement of MHT (baseline), and reassessed at varying intervals over the course of the treatment. Delta-PSQI indicates the difference between the baseline and follow-up score. Each subject's score in the follow-up assessment was matched with their own baseline score. Comparisons were made using one-way ANOVA followed by Tukey's HSD post-hoc test. P-values at each follow-up are as compared to values at baseline, with a value of $P<0.05$ considered to indicate a statistically significant difference with a value of $P<0.05$ considered to indicate a statistically significant difference. Some subjects had multiple assessments during a given interval. MHT, menopausal hormonal therapy; PSQI, Pittsburgh Sleep Quality Index; N/A, not available; ANOVA, analysis of variance; HSD, honestly significant difference; [a]Tukey's HSD post-hoc test: P-values at each follow-up are as compared to values at 1 month.

2.28 (0.67)-points difference compared to the initial score prior to the commencement of MHT ($P<0.005$).

In the small subgroup of 14 participants with a previous history of breast cancer, who were receiving tibolone MHT, no

Table III. Changes in KMI scores of the participants receiving MHT.

MHT period	No. of participants	Mean (±SD)	One-way ANOVA (P-value)	Tukey's HSD post-hoc test[a] (P-value)
0 days (baseline)	342	18.63 (9.86)		-
1st month	111	12.26 (8.09)		<0.0001
2nd month	107	11.38 (6.86)		<0.0001
3rd month	92	12.14 (7.60)		<0.0001
>3 months	169	11.16 (7.38)		<0.0001
>6 months	113	9.78 (7.59)	<0.0001	<0.0001
>9 months	84	10.67 (8.59)		<0.0001
>1 year	133	9.99 (7.37)		<0.0001
>2 years	76	10.52 (8.40)		<0.0001
>3 years	79	9.90 (7.33)		<0.0001

Comparisons were made against baseline KMI scores using one-way ANOVA followed by Tukey's HSD post-hoc test. P-values at each follow-up are as compared to values at baseline, with a value of P<0.05 considered to indicate a statistically significant difference. All 342 subjects received hormone treatment. KMI scores were assessed before starting MHT, and reassessed at varying intervals over the course of the treatment. Each subject's score in follow-up assessment was matched with their own baseline score. Some subjects had multiple assessments during a given interval. MHT, menopausal hormonal therapy; KMI, Kupperman Menopause Index; N/A, not available; ANOVA, analysis of variance; HSD, honestly significant difference; [a]Tukey's HSD post-hoc test: P-values at each follow-up are as compared to values at baseline.

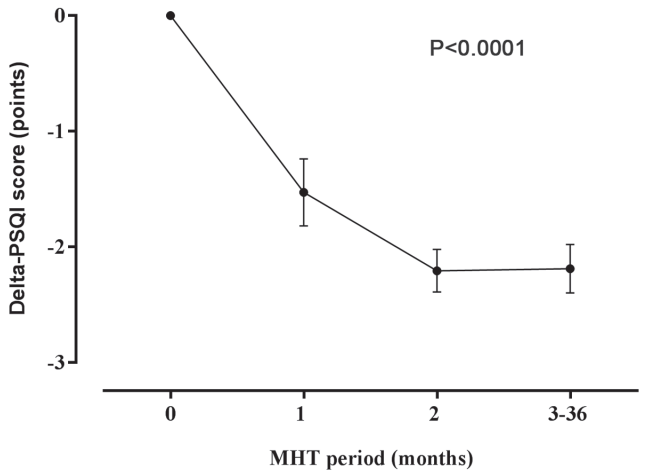

Figure 1. Effect of MHT on sleep quality. PSQI scores of study participants (n=76-342) were recorded prior to the commencement of MHT. The PSQI scores were then reassessed at varying intervals over the course of the treatment. Delta-PSQI indicates the difference between the initial and the follow-up score. Numbers are means ± SD; P<0.0001. MHT, menopausal hormonal therapy; PSQI, Pittsburgh Sleep Quality Index.

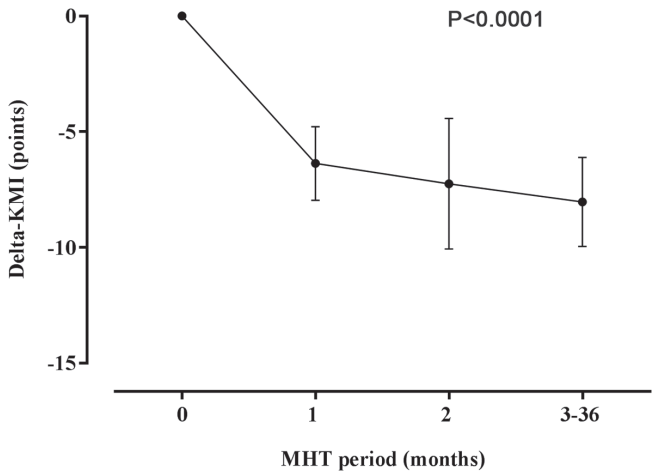

Figure 2. Effect of MHT on the KMI of the participants. KMI evaluation of menopausal symptoms was recorded prior to the commencement of MHT, and reassessed at varying intervals over the course of the treatment. Delta-KMI indicates the difference between the initial and the follow-up scores. n=76-342; numbers are the means ± SD; P<0.0001. MHT, menopausal hormonal therapy; KMI, Kupperman Menopause Index.

significant effect of the hormonal therapy was observed on the PSQI scores (P=0.956; Table VI).

Discussion

In the present study, we examined the effects of hormone replacement therapy on self-reported menopausal symptoms in general, and the quality of sleep of post-menopausal women in particular. The mechanisms through which estrogen/progestin therapies may improve sleep quality are not yet well known. A previous study using rodents suggested that estrogen consolidates circadian sleep-wake rhythms in female rats (24). Alternatively, the effects of estradiol on sleep/wake cycles may be explained by a reduction in prostaglandin synthesis in the ventrolateral preoptic nucleus of the hypothalamus (25). It is also possible that estrogen therapy may improve sleep quality indirectly, by relieving nocturnal hot flashes (26). In this study, it was found that MHT induced a rapid decrease in the PSQI scores as early as 1 month after the commencement of therapy. Sleep improvement further continued through the 2nd month of MHT, resulting in a >1.3-fold decrease in the PSQI score compared to the baseline assessment. Notably, after the initial improvement of the PSQI scores achieved after 2 months of MHT, there was no further significant improvement in sleep quality, with the PSQI scores maintaining the same decrease of 2.19 points compared to baseline.

Table IV. Changes in MRS scores of the in participants receiving MHT.

MHT period	No. of participants	Mean (±SD)	One-way ANOVA (P-value)	Tukey's HSD post-hoc test[a] (P-value)
0 days (baseline)	342	8.66 (6.17)		-
1st month	111	5.10 (4.67)		<0.0001
2nd month	107	4.64 (4.20)		<0.0001
3rd month	92	4.93 (4.26)		<0.0001
>3 months	169	4.93 (4.32)	<0.0001	<0.0001
>6 months	113	4.22 (3.83)		<0.0001
>9 months	84	4.32 (5.68)		<0.0001
>1 year	133	3.47 (3.35)		<0.0001
>2 years	76	4.04 (4.09)		<0.0001
>3 years	79	4.70 (4.60)		<0.0001

Comparisons were made against baseline MRS scores using one-way ANOVA followed by Tukey's HSD post-hoc test. P-values at each follow-up are as compared to values at baseline, with a value of P<0.05 considered to indicate a statistically significant difference. All 342 subjects received hormone treatment. MRS scores were assessed before starting MHT, and reassessed at varying intervals over the course of the treatment. Each subject's score in follow-up assessment was matched with their own baseline score. Some subjects had multiple assessments during a given interval. MHT, menopausal hormonal therapy; MRS, menopause rating scale; N/A, not available; ANOVA, analysis of variance; HSD, honestly significant difference; [a]Tukey's HSD post-hoc test: P-values at each follow-up are as compared to values at baseline.

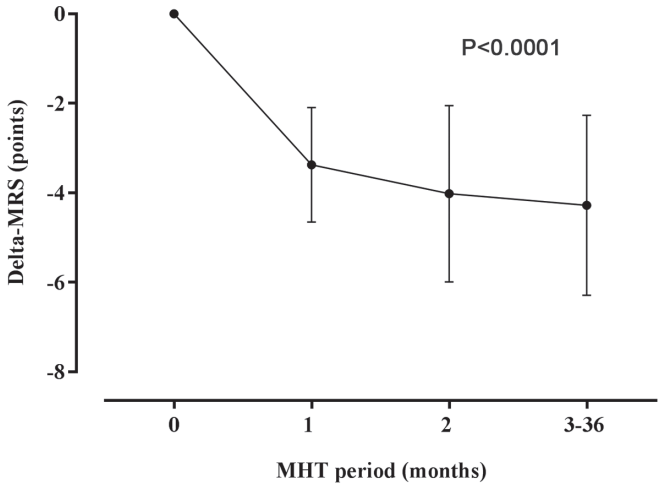

Figure 3. Effect of MHT on menopausal rating scale scores. The menopausal symptoms of the study participants (n=76-342) were assessed using MRS. Initial MRS score was prior to the commencement of MHT, and reassessed at varying intervals over the course of the treatment. Delta-MRS indicates the difference between the initial and the follow-up scores. Numbers are the means ± SD; P<0.0001. MHT, menopausal hormonal therapy; MRS, menopause rating scale.

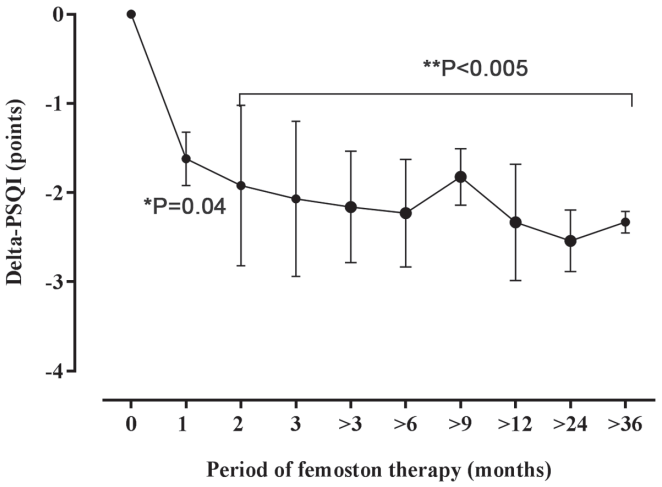

Figure 4. Effect of femoston MHT on sleep quality. Sleep quality of the subgroup of participants receiving femoston (n=72-328) was assessed using the PSQI. The initial score was recorded before the beginning of femoston treatment, and reassessed at varying intervals over the course of the treatment. Delta-PSQI indicates the difference between the initial and the follow-up scores. Numbers are the means ± SD; *P=0.04; **P<0.005. MHT, menopausal hormonal therapy; PSQI, Pittsburgh Sleep Quality Index.

In this study, the dynamics of sleep quality improvement observed in participants receiving MHT, coincided with a similar pattern of overall improvement in menopausal symptoms, as indicated by the KMI and MRS scores. It was demonstrated, that similar to the PSQI scores, patients reported the most significant decrease in the severity of menopausal symptoms during the first months of MHT. A major improvement was reported by the 2nd month of therapy. Prolonged treatment did not result in any further alleviation of symptoms, although it rather helped to maintain the KMI and MRS scores that were decreased during the initial months of hormone replacement therapy. While the precise mechanisms through which menopausal transition affect sleep quality remain unclear, previous studies have demonstrated that symptoms, such as nocturnal hot flashes, mood disorders and sleep-disordered breathing are the main contributors to a poor sleep quality (9,27-29). It is possible, therefore, that the immediate partial relief of these symptoms by hormone replacement therapy may have led to a similarly rapid improvement in the sleep quality of the participants.

There is still limited evidence as regards the effects of a conventional estrogen/progestin MHT, such as femoston, on sleep quality. It has been demonstrated that progesterone may have a sedative effect (30), and estrogen is able to increase

Table V. Changes in PSQI scores of patients receiving femoston.

MHT period	No. of participants	Mean (±SD)	One-way ANOVA (P-value)	Tukey's HSD post-hoc test[a] (P-value)
0 days (baseline)	328	9.14 (4.84)		-
1st month	105	7.52 (4.50)		0.04
2nd month	105	6.88 (4.47)		0.0002
3rd month	88	7.07 (3.98)		0.0047
>3 months	166	6.90 (4.30)	<0.0001	<0.0001
>6 months	110	6.85 (4.31)		0.0001
>9 months	76	7.30 (4.46)		0.0417
>1 year	129	6.84 (4.15)		<0.0001
>2 years	72	6.61 (4.52)		0.0006
>3 years	78	6.81 (4.72)		0.0015

Comparisons were made against baseline PSQI scores using one-way ANOVA followed by Tukey's HSD post-hoc test. P-values at each follow-up are as compared to values at baseline, with a value of P<0.05 considered to indicate a statistically significant difference. All 328 subjects received MHT with femoston. PSQI scores were assessed before starting MHT, and reassessed at varying intervals over the course of the treatment. Each subject's score in follow-up assessment was matched with their own baseline score. Some subjects had multiple assessments during a given interval. MHT, menopausal hormonal therapy; PSQI, Pittsburgh Sleep Quality Index; N/A, not available; ANOVA, analysis of variance; HSD, honestly significant difference; [a]Tukey's HSD post-hoc test: P-values at each follow-up are as compared to values at baseline.

Table VI. Changes in PSQI scores of participants receiving tibolone.

MHT period	N	Mean (±SD)	One-way ANOVA (P-value)	Tukey's HSD post-hoc test[a] (P-value)
0 days (baseline)	14	9.57 (5.00)		-
1st month	6	9.50 (5.96)		1.09
2nd month	3	10.33 (5.51)		1
3rd month	5	6.20 (4.92)		0.93
>3 months	5	8.80 (5.02)	0.956	1
>6 months	3	10.00 (4.58)		1
>9 months	8	8.00 (4.17)		0.99
>1 year	5	8.60 (4.83)		1
>2 years	4	8.25 (3.95)		1
>3 years	1	14 (N/A)	-	-

Comparisons were made against baseline PSQI scores using one-way ANOVA followed by Tukey's HSD post-hoc test. P-values at each follow-up are as compared to values at baseline, with a value of P<0.05 considered to indicate a statistically significant difference. All 14 subjects were treated with tibolone. PSQI scores were assessed before starting MHT, and reassessed at varying intervals over the course of the treatment. Each subject's score in follow-up assessment was matched with their own baseline score. Due to the low number of cases where tibolone was administered, statistical analysis could not be applied to some intervals and have low validity for others. MHT, menopausal hormonal therapy; PSQI, Pittsburgh Sleep Quality Index; N/A, not available; ANOVA, analysis of variance; HSD, honestly significant difference; [a]Tukey's HSD post-hoc test: P-values at each follow-up are as compared to values at baseline.

overall sleep time, and decrease sleep onset latency (31), and awakening after sleep onset (32). In this study, femoston was found to have a marked and rapid effect on self-reported sleep quality, with the PSQI score decreasing 1.32-fold during the first 2 months of the treatment. This decrease was maintained throughout the 3 years of the study period, suggesting that estrogen/progestin MHT results in a stable improvement of sleep quality. Of note, MHT with tibolone did not improve sleep quality in a small group of participants with a previous history of breast disease. Tibolone is a synthetic steroid that has progestogenic, androgenic, and estrogenic effects, shown to improve insomnia via stimulation of the production and release of β-endorphin (33,34). It is possible that the lack of an effect of tibolone on sleep quality in this study is related to an insufficient number of participants receiving this MHT. Better designed, larger clinical studies are thus required to examine the efficiency of tibolone in improving the sleep quality of menopausal women.

In conclusion, this study found that hormone replacement therapy had an immediate and long-lasting positive effect on sleep quality and on the general well-being of women

experiencing menopausal symptoms. While a conventional estrogen/progestin MHT with femoston resulted in a marked improvement of sleep quality, tibolone treatment had no effect on the PSQI score. Further clinical studies with larger patient groups are required to compare the effects of both MHT regiments on sleep quality.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CL and XY conceived and designed the study. CL, LW and XS provided the study materials or patient data and were responsible for the collection and assembly of the data, data analysis and interpretation. CL was involved in the writing of the manuscript. XY was involved in the editing of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of the Maternity and Child Health Care of Zaozhuang approved this retrospective medical record review (approval no. 2016006).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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