

Sleep quality and fatigue in women with premature ovarian insufficiency receiving hormone therapy: a comparative study

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Abstract

Objective: To compare sleep quality and fatigue between women with premature ovarian insufficiency (POI) receiving hormone therapy (HT) and women of the same age with preserved ovarian function.

Methods: This was a cross-sectional study of 61 women with POI receiving HT (POI group) and 61 women with preserved ovarian function (control group) who were matched by age (± 2 years). The Pittsburgh Sleep Quality Index (PSQI) and Chalder Fatigue Scale were used to assess sleep quality and fatigue. Apart from correlation analysis, the Mann-Whitney, chi-square, or Fisher test was used to compare the groups.

Results: Women from the POI and control groups were 35.03 ± 7.68 and 34.49 ± 7.55 years of age, respectively ($P = 0.63$). In the PSQI evaluation, the scores were 7.69 ± 4.18 and 8.03 ± 4.53 , respectively ($P = 0.79$), showing no difference between the POI and control groups. However, the POI group had higher and therefore worse scores for the sleep latency component (1.74 ± 0.66 and 1.18 ± 0.87 , respectively; $P < 0.001$) and use of medication to sleep (1.28 ± 0.88 and 0.85 ± 0.8 ; $P = 0.008$). The POI group had a higher fatigue index than that of the control group (5.25 ± 2.78 and 3.49 ± 1.78 , respectively; $P < 0.001$), with sleep quality being classified as poor in 69% and fatigue present in 59% of patients.

Conclusions: Women with POI receiving HT have poor sleep quality. They take longer to fall asleep and have a higher fatigue index.

Key Words: Fatigue – Hormone therapy – Premature ovarian insufficiency – Sleep quality.

The prevalence of complaints related to sleep is clearly greater in women than in men, contributing to fatigue and poor quality of life.¹ There are indications that sleep disturbances can manifest at any stage of life, but in women, the prevalence increases with the onset of the climacteric, regardless of the presence of chronic comorbidities, which worsens sleep quality.^{2,3}

Thus, sleep disturbances are one of the most frequent complaints of women in the menopausal and postmenopausal transition,⁴ with a prevalence of 40% to 56%, considering self-reports of sleep difficulty, even when such data are

controlled and adjusted for age.⁵ Common symptoms of perimenopause (sweating and hot flashes) associated with decreased estrogen levels may influence this condition; however, sleep difficulties may be present notwithstanding these symptoms.^{2,3} Studies evaluating the prevalence of sleep continuity disturbances in women during the menopausal transition reported difficulties in falling asleep (57.8%), difficulties in staying asleep (70%), and reports of waking up too early (60.7%).^{6,7} Women with insomnia generally complain about body pain, headaches, daytime dysfunction, decreased work productivity, mood disorders, and fatigue, which can negatively influence their quality of life.⁷ There are also indications that surgical menopause is associated with more severe sleep disturbances than natural menopause,^{5,8-11} especially when hormone therapy (HT) is not used, highlighting the fact that the use of HT effectively improves sleep quality.¹² It can further be said that sleep is a physiological state that deteriorates with age, with a progressive decrease in quantity and quality; for example, sleep disruption, fewer slow-wave sleep, and less rapid eye movement sleep.⁷

Chronic fatigue is a complaint often reported by patients in primary health care and has, for years, been reported as an important public health issue.¹³ It is multifactorial and considered chronic when it persists for at least 6 months, and it is accompanied by various physical and psychosocial symptoms.¹⁴ Some studies have indicated that higher levels of fatigue are directly related to psychological and physical suffering.¹⁵⁻¹⁷ In

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addition, it is one of the most common and distressing symptoms linked with menopause. There are data suggesting that 85.3% of postmenopausal women and 46.5% of women in menopausal transition report symptoms of physical and mental exhaustion compared with only 19.7% of premenopausal women.¹⁸

A specific group of women presenting with early-onset chronic hypoestrogenism develop premature ovarian insufficiency (POI).¹⁹ No study in the literature has evaluated the quality of sleep in this group of women. Therefore, this study aimed to compare the quality of sleep and fatigue between women with POI receiving HT and women of the same age with preserved ovarian function.

METHODS

This cross-sectional quantitative study was conducted in the Department of Obstetrics and Gynecology of the Faculty of Medical Sciences at the University of Campinas with inclusion of participants from June, 2016 to September, 2017.

One hundred twenty-two women aged 18 to 45 years were included, 61 of whom were diagnosed with POI and treated with HT (POI group), and the remaining 61 women had preserved ovarian function (the control group), matched by age (± 2 years) to the POI group.

Patients were diagnosed with POI when they presented with hypergonadotropic hypogonadism before 40 years of age and had an elevated follicle-stimulating hormone level (>25 mIU/mL) on two or more occasions.¹⁹ At the time of inclusion, all women had to receive estrogen plus progesterone therapy prescribed according to their individual needs. The women in the control group had preserved ovarian function, and to characterize normal function, patients had to have regular monthly menstrual cycles²⁰ and not be using hormones or other drugs that could alter steroidogenesis. A history of cancer; liver, kidney, or respiratory insufficiencies; chemotherapy or radiotherapy; or cognitive deficiency or illiteracy that would make it impossible to understand the questionnaires were considered exclusion criteria for both groups.

A personal interview was conducted to collect data. The numerical variables were age, number of living children, and number of miscarriages. The categorical variables were presence of children (yes or no), history of miscarriages (yes or no), marital status (whether they were in a stable relationship), and psychological or psychiatric counseling (yes or no); these data were analyzed and correlated to sleep and fatigue in the POI group. The POI diagnosis period (time in years from diagnosis to inclusion in the study) and duration of HT treatment were also analyzed for only the POI group.

The research was approved by the Ethics Committee of the institution (CAEE number: 61821516.0.000.5404), and all women signed an informed consent form.

Sleep quality assessment

The Pittsburgh Sleep Quality Index (PSQI) was administered to evaluate the quality of sleep over 1 month. The questionnaire consisted of 19 self-evaluation questions and five questions directed to the spouse or room companion; the

latter did not contribute toward the general index score. The 19 individual items generated seven component scores, with scores ranging from 0 (no difficulty) to 3 (great difficulty). The components are subjective sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4) (repairing or not), sleep disturbances (C5), use of sleeping medication (C6), and daytime dysfunction (C7).

The sum of scores for these seven components yields one global score that can range from 0 to 21 points, and the higher the score, the lower the quality of sleep. A score of 5 points or more corresponds to poor sleep quality, indicating that the individual presents major dysfunctions in at least two components or moderate dysfunction in at least three components.^{21,22}

Fatigue assessment

The Chalder Fatigue Scale was utilized; it contains 14 closed-ended multiple-choice questions and covers physical symptoms, such as fatigue and lack of energy, and considers mental symptoms, such as the lack of concentration, interest, and memory. The questionnaire was administered using the bimodal response system, employing the General Health Questionnaire method,²³ and the score can vary from 0 to 14 points. Fatigue is defined as a total score ≥ 4 .^{15,24}

Statistical analysis

Because of a lack of studies regarding sleep quality in women with POI, the convenience sample included women with POI who visited the institution between June, 2016 and September, 2017, and met the aforementioned inclusion criteria. The power of the sample was calculated for variables that showed a significant difference between the groups, considering the current sample size and 5% significance.

To compare qualitative variables between the two groups, the chi-square or Fisher exact test was used. The Mann-Whitney test was used to compare continuous variables between the two groups because these data lacked a normal distribution. The Spearman correlation coefficient was calculated in the correlation analysis of continuous variables. Significance was set at 5%. Statistical analysis was performed using the SAS System for Windows, version 9 (SAS Institute).

RESULTS

The mean ages of women with POI receiving HT ($n = 61$) and those in the control group ($n = 61$) were 35.03 ± 7.68 and 34.49 ± 7.55 years, respectively, with no difference between the groups ($P = 0.63$). Women presenting with POI had been diagnosed 10.49 ± 7.44 years previously and had been receiving HT treatment for 7.84 ± 6.03 years, without hot flash symptoms. Regarding obstetric history, the mean number of children was 0.44 ± 0.92 in the POI group and 1.28 ± 1.38 children in the control group ($P = 0.001$). Seventy-five percent of the women in the POI group were nulliparous. In addition, there was no difference between the groups regarding the number of miscarriages or marital status (having a steady partner) or in the percentage of women undergoing psychological counseling (Table 1).

TABLE 1. Characterization of women with premature ovarian insufficiency receiving hormone therapy (POI with HT) and women with preserved ovarian function (control)

	POI group (n = 61)	Control group (n = 61)	P
Age	35.03 ± 7.68	34.49 ± 7.55	0.63 ^a
Number of children	0.44 ± 0.92	1.28 ± 1.38	0.001 ^a
Number of miscarriages	0.10 ± 0.40	0.07 ± 0.25	0.96 ^a
Steady partner (%)	78.60	77	0.82 ^b
Psychological follow-up (%)	16.30	22.90	0.36 ^b
Time of diagnosis (y)	10.4 ± 7.4		
Duration of HT (y)	7.84 ± 6.03		

Psychological follow-up—women in follow-up with psychologist or psychiatrist.

HT, hormone therapy; POI, premature ovarian insufficiency.

^aMann-Whitney test.

^bChi-square test.

In the evaluation of sleep quality by the PSQI, the scores were 7.69 ± 4.18 and 8.03 ± 4.53 for the POI and control groups, respectively ($P = 0.79$, with medians of 8.0 and 7.0, respectively), with no difference between the groups. However, considering that the cut-off level adopted to indicate poor sleeping quality for this scale is 5, it was verified that the average/mean scores pointed toward poor sleep quality in both groups. It was found that the percentages of poor sleepers (total score less than 5) were 69% in the POI group and 62% in the control group.

Although the groups did not differ in their total score, there was a difference between them regarding the components evaluated. Women with POI presented higher and thus worse scores for C2, which evaluates sleep latency (1.74 ± 0.66 and 1.18 ± 0.87 , respectively; $P < 0.001$), and C6, which evaluates the use of sleeping medication (1.28 ± 0.88 and 0.85 ± 0.8 , respectively; $P = 0.008$), indicating that they are more likely to take longer to fall asleep once they are in bed and to use more medication to sleep (Table 2).

Compared with women in the POI group, women in the control group rated themselves as having more impairment in subjective sleep quality (C1, with scores of 0.77 ± 1.01 vs 1.18 ± 0.87 ; $P = 0.004$); presenting sleep disturbances (C5, with scores of 0.66 ± 0.93 vs 1.10 ± 0.93 ; $P = 0.004$); and reporting daytime dysfunction, referred to as the difficulty to stay awake (C7, with scores of 0.33 ± 0.79 vs 0.61 ± 0.80 ; $P = 0.005$) (Table 2).

No differences were observed between the groups in the components that evaluate sleep duration (C3, with scores of 1.57 ± 1.04 and 1.80 ± 0.89 in the POI group and control group, respectively; $P = 0.253$) and habitual sleep efficiency (C4, with scores of 1.34 ± 1.01 and 1.31 ± 0.89 , respectively; $P = 0.99$) (Table 2).

Women with POI had higher fatigue indices, according to the Chalder scale, than those with preserved ovarian function (5.25 ± 2.78 vs 3.49 ± 1.78 points; $P < 0.001$, medians of 5.0 and 3.0). Considering fatigue characterization when the total score was ≥ 4 , fatigue was present in 59% of women in the POI group and 18% of women in the control group (Table 2). Among women with a total PSQI score ≥ 5 (poor sleep quality), 85% presented with fatigue, whereas when there was no sleep quality impairment, 60% of them did not present with fatigue.

The calculation of the sample power was 98% for sleep latency and the fatigue score, in addition to a sample power of 80% for the use of sleeping medication.

On the basis of the correction analysis, it was verified that the total sleep quality score of women in the POI group was directly correlated with the number of children, meaning that the greater the number of children, the worse the sleep quality ($r = 0.40$, $P = 0.001$); however, it was not correlated with age, the time of diagnosis, duration of hormone treatment, or number of miscarriages. Quality of sleep and fatigue were directly correlated in women with POI, showing that the worse the quality of sleep, the greater the fatigue ($r = 0.39$, $P = 0.001$). Fatigue rates were

TABLE 2. Total and component scores for the sleep quality questionnaire (Pittsburgh Sleep Quality Index) and fatigue for women with premature ovarian insufficiency receiving hormone therapy (n = 61) and for women with preserved ovarian function (n = 61)

	POI group		Control group		P ^a
	Mean ± SD	and median	Mean ± SD	and median	
PSQI	7.69 ± 4.18	8.0	8.03 ± 4.53	7.0	0.79
C1—subjective sleep quality	0.77 ± 1.01	0.0	1.18 ± 0.87	1.0	0.004
C2—sleep latency	1.74 ± 0.66	2.0	1.18 ± 0.87	1.0	<0.001
C3—sleep duration	1.57 ± 1.04	2.0	1.80 ± 0.89		0.253
C4—habitual sleep efficiency	1.34 ± 1.01	1.0	1.31 ± 0.89	1.0	0.099
C5—sleep disturbances	0.66 ± 0.93	0.0	1.10 ± 0.93	1.0	0.004
C6—use of sleeping medication	1.28 ± 0.88	1.0	0.85 ± 0.81	1.0	0.008
C7—daytime dysfunction	0.33 ± 0.79	0.0	0.61 ± 0.80	0.0	0.005
Fatigue	5.25 ± 2.78	5.0	3.49 ± 1.78	3.0	<0.001

Fatigue: Chalder Fatigue Scale; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

^aMann-Whitney test.

TABLE 3. Spearman correlation analysis between sleep quality and variables assessed for women with premature ovarian insufficiency receiving hormone therapy (n = 61)

	PSQI		Fatigue	
	R	P	R	P
Age	0.24	0.056	0.07	0.564
Time of Diagnosis	0.003	0.978	−0.24	0.058
Duration of HT	−0.05	0.661	−0.29	0.021
Number of Children	0.40	0.001	0.23	0.067
Miscarriages	0.11	0.393	0.33	0.008
Fatigue	0.39	0.001		

HT, hormone therapy; PSQI, Pittsburgh Sleep Quality Index.

also inversely correlated with the treatment period and directly correlated with the number of miscarriages ($r = -0.29$, $P = 0.021$; and $r = 0.33$, $P = 0.008$, respectively). Although not statistically significant, age showed a tendency toward a direct association with fatigue and sleep quality (Table 3). The same results were obtained in the multivariate linear regression analysis using the stepwise criteria for sleep quality (PSQI) and fatigue (Table 4).

DISCUSSION

Our results show that women with POI receiving HT have poor sleep quality, but it is similar to that of women of the same age with preserved ovarian function; however, the former presented with a higher rate of fatigue. Variables directly related to ovarian insufficiency, such as the diagnosis time or treatment time, were not related to sleep; nevertheless, it was found that the greater the number of children, the worse the quality of sleep.

Although our results show no difference in self-reported sleep quality among women with POI using HT and women of the same age with preserved ovarian function, the percentage of poor sleepers can be highlighted in both groups. Sleep is vital to health. Sleep disturbances are associated with adverse physical and mental conditions; that is, they have an impact on brain function including cognitive function, memory consolidation, mood, metabolism, appetite, immune functions, the cardiovascular system, and hormonal fluctuations. There are even indications of an association between short sleep duration and an increase in mortality; however, this relationship is not yet fully understood.²⁵

Although complaints of insomnia are common during all stages of life, studies showed that sleep difficulties are particularly associated with menopausal transition. The latter is a period in which hormonal fluctuations occur,⁸ causing symptoms such as hot flashes that are considered the greatest factor that contributes toward the complaint of sleep deterioration in this life stage and has an inverse correlation with sleep quality.^{12,26,27} Although the effects of menopausal HT on sleep quality are unclear, there is evidence that effective treatment of hot flashes is associated with improved sleep quality in perimenopausal women.^{9,28} A recent study showed that sleep quality and insomnia in women in menopausal and postmenopausal transition improved markedly shortly after the first month of hormonal treatment.²⁹ In addition, sleep is a physiological state that deteriorates with age, with progressive reduction in its quality and quantity⁷—a factor that contributes to insomnia complaints in the perimenopausal period. On the basis of this, it is possible to presume that the similar PSQI scores for the POI and control groups may have been influenced by the fact that women with POI are younger than postmenopausal women and they do not have hot flash symptoms because of the use of HT.

Interestingly, our results showed that the higher the number of children, the worse the quality of sleep in women with loss of ovarian function. It is a well-known fact that women usually face a double work shift when working outside the home³⁰ and that the prevalence of complaints related to sleep is more frequent in women than in men.¹

The fatigue factor has been evaluated less than sleep quality. Women in perimenopause present with greater fatigue than

TABLE 4. Multivariate linear regression analysis using stepwise criteria for sleep quality (Pittsburgh Sleep Quality Index) and fatigue in women with premature ovarian insufficiency receiving hormone therapy (n = 61)

	Beta (EP) ^a	P	Partial R ²
Selected variables for sleep quality (PSQI)			
Number of children	0.44 (0.15)	0.006	0.1634
Fatigue	0.32 (0.12)	0.009	0.0948
Selected variables for fatigue			
Number of miscarriages	0.77 (0.27)	0.005	0.1125
Duration of treatment (y)	−0.29 (0.12)	0.016	0.0855

Stepwise selection of variables. R² Total: 0.2582. Intercept (EP): 7.61 (5.63); $P = 0.182$. Variables without normal distribution were transformed into stations/ranks.

EP, standard error of beta; R², coefficient of determination.

^aValue of the estimate or slope in the regression line.

those who are not in this period (prevalence of up to 85%). In women with POI receiving HT, the prevalence was 59%; therefore, more causal research is necessary.

Premature ovarian insufficiency causes physical and psychological effects resulting from hypoestrogenism, such as the loss of fertility, bone loss, an increased cardiovascular risk, psychological disturbances, altered sexuality, and even the risk of earlier mortality.¹⁹ The treatment must minimize such repercussions. One of the seemingly overlooked or unknown aspects is the repercussion of early hypoestrogenism on sleep quality and fatigue, and also the extent to which HT can act on these aspects.

Although it is not possible to reach conclusions regarding cause and effect in a cross-sectional study, to the best of our knowledge, this is the first study to evaluate the sleep quality in women with POI. It is necessary to highlight the difficulty and variability in the definition of sleep quality. Thus, many studies use reports with individual meaning and subjective criteria that may be related to an individual's perception of factors, such as fatigue during the day, a sensation of feeling rested upon waking, or the number of times that they wake up at night.^{31,32} The PSQI—an accepted and validated specific questionnaire to evaluate sleep—has been used in studies showing that specific questionnaires are highly predictive in terms of sleep quality.³³ In addition, we included a homogeneous group of women, all who received HT and who had no other serious chronic diseases. However, we used an age-matched control group, thus reducing the impact of this factor in the analysis.

Thus, the results show that it is imperative to reinforce the need to discuss and evaluate sleep quality when treating women with POI.

CONCLUSIONS

In addition to having higher rates of fatigue, women with POI receiving HT have poor sleep quality, have greater difficulty falling asleep, and use more sleep-inducing medications compared with women of the same age with preserved ovarian function.

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