

# A multicentric study regarding the use of hormone therapy during female mid-age (REDLINC VI)

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## ABSTRACT

**Background** Menopausal hormone therapy (HT) has shown benefits for women; however, associated drawbacks (i.e. risks, costs, fears) have currently determined its low use.

**Objective** To determine the prevalence of current HT use among mid-aged women and describe the characteristics of those who have never used, have abandoned or are currently using HT. In addition, reasons for not using HT were analyzed.

**Method** This was a cross-sectional study that analyzed a total of 6731 otherwise healthy women (45–59 years old) of 15 cities in 11 Latin American countries. Participants were requested to fill out the Menopause Rating Scale (MRS) and a questionnaire containing sociodemographic data and items regarding the menopause and HT use.

**Results** The prevalence of current HT use was 12.5%. Oral HT (43.7%) was the most frequently used type of HT, followed by transdermal types (17.7%). The main factors related to the current use of HT included: positive perceptions regarding HT (odds ratio (OR) 11.53, 95% confidence interval (CI) 9.41–14.13), being postmenopausal (OR 3.47, 95% CI 2.75–4.36) and having a better socioeconomic level. A total of 48.8% of surveyed women had used HT in the past, but abandoned it due to symptom improvement or being unconcerned; fear of cancer or any other secondary effects were also reported but in less than 10%. Among women who had never used HT, 28% reported the lack of medical prescription as the main reason, followed by the absence of symptoms (27.8%). Among those reporting lack of prescription as the main reason for not using HT, 30.6% currently had severe menopausal symptoms (total MRS score > 16); 19.5% of women were using alternative ‘natural’ therapies, with 35.1% of them displaying severe menopausal symptoms as compared to a 22.5% observed among current HT users.

**Conclusion** The use of HT has not regained the rates observed a decade ago. Positive perceptions regarding HT were related to a higher use. Lack of medical prescription was the main reason for not using HT among non-users, many of whom were currently displaying severe menopausal symptoms.

## INTRODUCTION

The climacteric is a period of a woman’s life characterized by a series of clinical events related to the decline and cessation of ovarian function. These events include an array of symptoms such as mood disorders, poor quality of sleep,

musculoskeletal aches and vasomotor symptoms, which may appear several years before the menopause and in some women continue decades after<sup>1</sup>. These symptoms significantly impair female quality of life<sup>2</sup>.

Hormone therapy (HT) decreases menopausal symptoms and improves quality of life<sup>3</sup>. HT not only has effects on the

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typical menopausal symptoms observed early during the menopause but it also prevents vaginal atrophy and decreases the risk of urinary tract infections<sup>4</sup>. Moreover, it decreases cardiovascular risk factors<sup>5</sup> and can improve bone mass and reduce fracture risk<sup>6</sup>.

As a consequence of the well-known positive effects of estrogen therapy observed in the USA a decade ago, HT was used by up to 38.3% of women aged 50–59 years<sup>7</sup>. The publications of the results of the WHI study that demonstrated an increase in thrombotic risk and a slight increase in breast cancer risk among older users of oral estrogens and medroxyprogesterone resulted in a reduction in HT use<sup>8</sup>. A decade after the publication of the WHI results, HT use dropped to 6.7% among women aged 50–59 years<sup>7</sup>. Along with this decline in HT use was an increase in the prescription of alternative therapies for the menopause<sup>9</sup>. Subsequent studies have highlighted the fact that the WHI results were most likely related to the administration of oral conjugated estrogens to older women, who have a higher risk of thrombosis, and the use of medroxyprogesterone, a progestin that may cause a higher risk of breast cancer<sup>10</sup>. As a result of the WHI study, medical behaviors have changed, increasing the use of transdermal estrogen, a route that involves less risk of thrombosis. Moreover, initiation of HT use in the early postmenopausal phase would take advantage of the ‘window of opportunity’ in which estrogens would be cardioprotective<sup>11,12</sup>. Similarly, there has been a strong tendency to abandon the use of medroxyprogesterone and encourage the use of progesterone, which would not increase breast cancer risk<sup>13</sup>. Although a better understanding of the WHI results has increased in recent years, HT use has not regained the rates observed prior to the publication of the study results. The aim of the present research was to determine the prevalence of current HT use among mid-aged women and to describe the characteristics of those who have never used, who have abandoned or are currently using HT. In addition, reasons for not using HT were analyzed. Prevalence of alternative therapy use and its relation to the severity of menopausal symptoms will also be analyzed.

## METHODS

### Study design and participants

This was a cross-sectional study carried out among otherwise healthy Hispanic women aged 45–59 years who accompanied patients attending 19 health-care centers from 15 cities with more than 500 000 inhabitants in 11 Latin American countries. The majority of participating centers were third-level, private or university run. Interviewers were medical residents of obstetrics and gynecology. Healthy status was defined according to the criteria of the National Center for Health Statistics<sup>14</sup>, as that enabling the performance of daily routine activities.

Women fulfilling the inclusion criteria were informed about the research (and its purposes) and, after providing written

consent in accordance with the Declaration of Helsinki<sup>15</sup>, they were requested to fill out the Menopause Rating Scale (MRS) and a questionnaire containing general sociodemographic data and that related to HT use. Women with an ethnic origin distinct from Hispanic (i.e. Afro-American or Amerindian) or with a mental or physical handicap impairing the capacity to understand the survey and/or providing answers were excluded. The research protocol was reviewed and approved by the Bioethics Committee of the Servicio de Salud Metroropolitano Sur (Santiago de Chile, Chile).

EPI-INFO statistical software (EPI-INFO 6.04, 2001, Centers for Disease Control and Prevention, Atlanta, GA, USA) was used to calculate a minimal sample size of 336 women per center considering that each covers an estimated population of 50 000 women within the studied age range<sup>16</sup> and assuming that 15% of them would be current HT users<sup>17</sup>, with an estimated 10% desired precision and a 95% confidence level. A minimum of 350 participants was requested for each center.

## Instruments and variables

### General data

In order to record all data, an itemized questionnaire was previously constructed and validated among 50 women before implementation at the Latin American centers affiliated to the REDLINC (Collaborative Group for Research of the Climacteric in Latin America).

### Studied variables

Data included: age (years), weight (kg), height (cm), abdominal circumference (cm), body mass index (BMI, kg/height<sup>2</sup>), obesity (BMI  $\geq$  30 kg/m<sup>2</sup>), educational level (expressed in years), access to paid health-care system (yes/no), currently has stable partner (yes/no), menopausal status (pre-, peri- or postmenopausal), surgical menopause (yes/no), HT use (yes/no), alternative therapy use (yes/no), sexually active in the past 12 months (yes/no), hypertension (blood pressure > 140/90 mmHg and/or use of antihypertensive medication), diabetes mellitus (baseline glycemia > 125 mg/dl and/or the use of anti-diabetic agents).

### The Menopause Rate Scale

The Menopause Rate Scale (MRS) is an instrument composed of 11 items that assess menopausal symptoms<sup>18</sup> divided into three subscales: (1) *somatic*: hot flushes, heart discomfort, sleeping problems and muscle and joint problems (items 1–3 and 11, respectively); (2) *psychological*: depressive mood, irritability, anxiety and physical and mental exhaustion (items 4–7, respectively); and (3) *urogenital*: sexual problems, bladder problems and dryness of the vagina (items 8–10, respectively). Each item can be graded by the subject from 0 (not present) to 4 (1 = mild; 2 = moderate; 3 = severe; 4 = very

severe). A mean  $\pm$  standard deviation value can be obtained for each item. For a particular individual, the total score per each subscale is the sum of each graded item contained in that subscale. The total MRS score is the sum of the scores obtained for each subscale. Higher scores are indicative of more intense symptoms and hence more impaired quality of life. A total MRS score of  $> 16$  was defined as severe (severe menopausal symptoms/impaired quality of life)<sup>19</sup>. The MRS has been translated to more than 27 languages<sup>20</sup>, validated in the Spanish language<sup>21</sup> and used in many Latin American countries<sup>22</sup>.

## Statistical analysis

Data analysis was performed using the EPI-INFO statistical program (Version 7.1.0.6, 2012, Centers for Disease Control and Prevention, Atlanta, GA, USA; WHO, Basel, Switzerland). Results are presented as mean  $\pm$  standard deviations, percentages (95% confidence intervals) and odds ratios. The Kolmogorov–Smirnov test was used to assess the normality of data distribution and the Bartlett test to evaluate the homogeneity of the measured variance. According to this, group comparisons were performed with the Student's *t*-test (parametric continuous data) or the Mann–Whitney *U*-test (non-parametric continuous data). According to the case, percentages between groups were evaluated with the  $\chi^2$  test or Fisher's exact test.

Logistic regression analysis was performed to determine the factors influencing current HT use. HT use was considered as the dependent variable and the following as independent

variables: age ( $> 50$  years), postmenopausal status, surgical menopause, having a stable partner, sexually active, use of alternative therapies, access to paid health care, higher educational level ( $> 6$  years), obesity (BMI  $\geq 30$  kg/m<sup>2</sup>), presence of diabetes mellitus or hypertension, the perception of HT as 'good', and considering that the menopause affects quality of life. Entry of variables into the regression model was performed using a stepwise procedure and considering a 20% significance level. Interactions between significant variables found during regression model construction were also considered for the final model. Adequacy of the regression model was demonstrated with the Hosmer–Lemeshow goodness-of-fit test. For all calculations a *p* value of  $< 0.05$  was considered as statistically significant.

## RESULTS

A total of 13.1% ( $n = 6731$ ) of surveyed women were current HT users (Table 1). As compared to past and current HT users, it was observed that never users were younger, heavier, less educated, accessed paid health care at a lower rate and displayed higher BMI, abdominal circumference and rate of obesity. Past users displayed slightly higher anthropometric indices than the other two groups. The percentage of women with diabetes was higher among past users as compared to never and current HT users (16.3% vs. 14.1% and 12.3%, respectively,  $p < 0.006$ ). Prevalence of hypertension among past HT users was similar to that among never and current users (29.5% vs. 30.1% and 27.8%, respectively, not significant). In addition, never users, as compared to past and

**Table 1** General characteristics of the studied population according to use of hormone therapy (HT) ( $n = 6731$ ). Data are given as mean  $\pm$  standard deviation or % (95% confidence interval)

Characteristic	Never users ( $n = 2602$ , 38.7%)	Past users ( $n = 3286$ , 48.4%)	<i>p</i> Value*	Current HT users ( $n = 843$ , 12.5%)	<i>p</i> Value*
Age (years)	51.2 $\pm$ 4.3	51.4 $\pm$ 4.3	0.04 <sup>a</sup>	52.2 $\pm$ 4.1	0.0001 <sup>a</sup>
Weight (kg)	68.4 $\pm$ 11.9	69.2 $\pm$ 12.5	0.007 <sup>b</sup>	67.4 $\pm$ 12.4	0.04 <sup>a</sup>
Height (cm)	158.6 $\pm$ 6.8	158.8 $\pm$ 6.5	NS	159.6 $\pm$ 6.2	0.0001 <sup>b</sup>
Body mass index (kg/m <sup>2</sup> )	27.2 $\pm$ 4.7	27.5 $\pm$ 4.9	0.04 <sup>a</sup>	26.5 $\pm$ 4.6	0.0001 <sup>a</sup>
Abdominal circumference (cm)	85.9 $\pm$ 13.7	88.1 $\pm$ 13.1	0.0001 <sup>b</sup>	84.8 $\pm$ 13.0	0.03 <sup>a</sup>
Obesity prevalence	24.8 (23.1–26.5)	27.2 (25.7–28.7)	0.04 <sup>c</sup>	19.3 (16.8–22.2)	0.001 <sup>c</sup>
Diabetes	14.1 (12.8–15.5)	16.3 (15.5–18.0)	0.006 <sup>c</sup>	12.3 (10.2–14.1)	NS
Hypertension	30.1 (28.3–31.9)	29.5 (28.0–31.1)	NS	27.8 (24.8–30.9)	NS
Achieved educational level (years)	10.3 $\pm$ 4.6	11.2 $\pm$ 4.6	0.000 <sup>b</sup>	12.0 $\pm$ 4.5	0.0001 <sup>a</sup>
Payment for medical care	41.0 (39.2–43.0)	46.1 (44.4–47.8)	0.0001 <sup>c</sup>	55.8 (52.3–59.1)	0.0001 <sup>c</sup>
Postmenopausal	56.0 (54.1–57.9)	59.2 (57.5–60.9)	0.01 <sup>c</sup>	79.1 (76.2–81.8)	0.0001 <sup>c</sup>
Surgical menopause	14.1 (12.8–15.7)	19.1 (17.8–20.5)	0.0001 <sup>c</sup>	31.1 (28.0–34.3)	0.0001 <sup>c</sup>
With stable partner	71.0 (69.2–72.8)	73.9 (72.4–75.4)	0.01 <sup>c</sup>	79.7 (76.8–82.3)	0.0001 <sup>c</sup>
Sexually active <sup>†</sup>	69.7 (67.9–71.4)	69.9 (68.3–71.4)	NS	78.2 (75.2–80.9)	0.0001 <sup>c</sup>
MRS total score	11.6 $\pm$ 7.3	11.4 $\pm$ 7.2	NS	11.5 $\pm$ 6.9	NS
Women with severe MRS scores <sup>†</sup>	24.7 (23.1–26.4)	25.4 (23.9–26.9)	NS	22.5 (19.8–25.5)	NS

\*, *p* value as compared to never users as determined by Student's *t*-test<sup>a</sup>, Mann–Whitney test<sup>b</sup> or  $\chi^2$  test<sup>c</sup>; †, severe MRS scores: a total MRS score of  $> 16$ ; ‡, sexually active in the past 12 months

MRS, Menopause Rating Scale; BMI, body mass index; obesity: BMI  $\geq 30$  kg/m<sup>2</sup>; NS, non-significant

current users, displayed lower rates of postmenopause (56.0% vs. 59.2% and 79.1%, respectively,  $p < 0.01$ ), surgical menopause (14.1% vs. 19.1% and 31.1%, respectively,  $p < 0.0001$ ) and having a stable partner (71.0% vs. 73.9% and 79.7%, respectively,  $p < 0.01$ ). The rate of sexually active women was almost 10% higher among current HT users than among never and past users (78.2% vs. 69.7% and 69.9%,  $p < 0.01$ ). Regarding menopausal symptoms, total MRS scores and rate of severe MRS scores were similar among studied groups.

Perceptions regarding the menopause among surveyed women are displayed in Table 2. It was found that 74.9% of them perceived that the menopause affects female physical and psychological well-being; but this percentage varied significantly according to HT use. Indeed, while 74.9% of never HT users support this belief, this rate increases to 90.2% among current HT users ( $p < 0.01$ ). Moreover, menopausal symptoms are more intense among women affirming that the menopause impairs physical and psychological well-being (total MRS score  $12.0 \pm 7.3$  vs.  $10.0 \pm 6.8$ ,  $p < 0.0001$ ). Although three out of four women are aware that menopausal treatments exists, this rate varies significantly according to HT use. Indeed, while 68% of never users acknowledge the existence of menopausal treatments, this rate increases to 90.2% among current HT users. Women who are aware of the existence of treatments for the menopause in fact have less intense menopausal symptoms (total MRS score  $11.2 \pm 7.3$  vs.

$12.3 \pm 7.1$ ,  $p < 0.0001$ ) (Table 2). While 88% of current HT users affirm that the treatment of menopausal symptoms consists of the administration of hormones, this rate drops to 46.8% among never users ( $p > 0.01$ ), among whom 33% declared lacking knowledge regarding menopausal treatments. Finally, while 24.6% of never HT users declared that hormones are good, this rate increased to 79.8% among current users ( $p < 0.01$ ). Past users have perceptions positioned in between those of current and never users, except considering the use of natural therapies or physical exercise as main options for the management of menopausal symptoms.

The most frequently used type of HT among current users was oral HT (43.7%) followed by transdermal (17.7%) (Table 3). Vaginal, oral, transdermal and parenteral estrogen users displayed similar total MRS scores ( $12.2 \pm 6.6$  vs.  $11.6 \pm 7.0$ ,  $10.9 \pm 6.3$ , and  $13.0 \pm 6.8$ , respectively,  $p > 0.05$ ). Tibolone users displayed significantly lower MRS scores ( $9.8 \pm 7.4$ ,  $p < 0.002$ ). Total MRS scores were similar when current, never and past HT users were compared ( $11.5 \pm 6.9$  vs.  $11.6 \pm 7.3$  and  $11.4 \pm 7$ , respectively, not significant) (Table 1). Regarding HT use, it was found that 31% of current users had a history of surgical menopause in contrast to 14.1% among never users. Upon analyzing only women with surgical menopause, it was found that current HT users had significantly lower total MRS scores as compared to never users ( $11.9 \pm 7.0$  vs.  $12.9 \pm 7.0$ ,  $p < 0.04$ ).

**Table 2** Perceptions regarding the menopause and related symptoms in relation to hormone therapy (HT) use. Data are given as mean  $\pm$  standard deviation or % (95% confidence interval)

Answer options	All	Never users*	Past users	Current users	Menopausal symptoms <sup>†</sup>	
					Total MRS scores	Women with severe MRS scores
<i>Does the menopause affect women's physical and psychological well-being?</i>						
Yes	74.9 (7.9–75.9)	71.4 (69.6–73.1)	73.7 (72.0–75.8) <sup>NS</sup>	90.2 (87.9–92.0) <sup>a</sup>	$12.0 \pm 7.3$ <sup>†</sup>	26.7 (25.5–28.0) <sup>†</sup>
No	25.1 (24.1–26.2)	28.6 (26.9–30.4)	26.3 (24.8–27.9) <sup>NS</sup>	9.8 (8.0–12.1) <sup>a</sup>	$10.0 \pm 6.8$ <sup>b</sup>	19.0 (17.2–21.0) <sup>d</sup>
<i>Are there treatments for the management of menopausal symptoms?</i>						
Yes	74.8 (73.9–75.9)	68.0 (66.2–69.8)	76.0 (74.5–77.5) <sup>a</sup>	91.2 (89.1–93.0) <sup>a</sup>	$11.2 \pm 7.3$ <sup>†</sup>	23.6 (22.5–24.8) <sup>†</sup>
No	25.2 (24.1–26.2)	32.0 (30.2–33.8)	24.0 (22.5–25.5) <sup>a</sup>	8.8 (7.0–10.9) <sup>a</sup>	$12.3 \pm 7.1$ <sup>b</sup>	28.2 (26.1–30.4) <sup>d</sup>
<i>Treatment options mainly include....?</i>						
Hormones	55.2 (54.0–56.4)	46.8 (44.9–48.7)	53.5 (51.7–55.2) <sup>NS</sup>	88.0 (85.6–90.1) <sup>a</sup>	$10.9 \pm 7.2$ <sup>†</sup>	22.7 (21.3–24.1) <sup>†</sup>
Other drugs	4.3 (3.9–4.8)	4.5 (3.7–5.4)	4.8 (4.1–5.6) <sup>NS</sup>	1.9 (1.1–3.1) <sup>a</sup>	$12.2 \pm 7.6$ <sup>b</sup>	29.9 (24.7–35.5) <sup>d</sup>
Natural products	10.7 (10.0–11.5)	10.6 (9.4–11.8)	13.0 (11.9–14.2) <sup>a</sup>	2.5 (1.6–3.8) <sup>a</sup>	$13.1 \pm 7.6$ <sup>b</sup>	33.3 (29.9–36.9) <sup>d</sup>
Physical exercise	3.7 (3.3–4.2)	3.3 (2.6–4.0)	4.5 (3.9–5.3) <sup>a</sup>	1.7 (0.9–2.8) <sup>a</sup>	$11.9 \pm 6.6$ <sup>c</sup>	25.8 (20.5–31.7) <sup>NS</sup>
Other therapies	1.5 (1.2–1.8)	1.5 (1.1–2.1)	0.7 (0.3–1.6) <sup>a</sup>	1.7 (1.3–2.2) <sup>NS</sup>	$11.3 \pm 6.8$ <sup>NS</sup>	22.5 (14.9–31.9) <sup>NS</sup>
Does not know	24.5 (23.5–25.6)	33.3 (31.5–35.2)	22.5 (21.1–24.0) <sup>a</sup>	5.2 (3.9–7.0) <sup>a</sup>	$11.8 \pm 7.1$ <sup>b</sup>	24.8 (22.8–27.0) <sup>NS</sup>
<i>Hormones for the menopause are.....?</i>						
Good	37.1 (35.9–38.3)	24.6 (22.9–26.3)	36.1 (34.4–37.7) <sup>a</sup>	79.8 (76.9–82.5) <sup>a</sup>	$10.4 \pm 7.0$ <sup>†</sup>	20.2 (18.6–21.8) <sup>†</sup>
Bad	13.9 (13.0–14.7)	13.3 (12.0–14.7)	16.2 (15.0–17.5) <sup>NS</sup>	6.4 (4.9–8.3) <sup>NS</sup>	$12.9 \pm 7.5$ <sup>b</sup>	29.2 (26.3–32.2) <sup>d</sup>
Does not know	49.0 (47.8–50.2)	62.1 (60.2–64.0)	47.7 (46.0–49.4) <sup>a</sup>	13.8 (11.5–16.3) <sup>a</sup>	$12.0 \pm 7.2$ <sup>c</sup>	27.0 (25.5–28.6) <sup>d</sup>

Significant  $p$  values for perception comparisons were determined with the  $\chi^2$  test<sup>a</sup> using never users as the reference group\*; significant  $p$  values for menopausal symptom comparisons were determined with the Mann–Whitney test<sup>b</sup> or Student's  $t$ -test<sup>c</sup> (MRS total scores) or the  $\chi^2$  test<sup>d</sup> (frequency of severe MRS scores) using a reference group<sup>†</sup>

NS, non-significant

**Table 3** Types of hormone therapy (HT) used and menopausal symptoms among current users. Data are given as mean  $\pm$  standard deviation or % (95% confidence interval)

Hormone therapy	n	% of women (95% confidence interval)	Menopausal symptoms	
			Total MRS score	Severe total MRS scores
Vaginal estrogens*	136	16.1 (13.7–18.8)	12.2 $\pm$ 6.6	25.0 (18.0–33.1)
Oral HT	368	43.7 (40.3–47.1)	11.6 $\pm$ 7.0 <sup>NS</sup>	23.1 (19.0–27.8) <sup>NS</sup>
Transdermal estrogens	149	17.7 (15.2–20.5)	10.9 $\pm$ 6.3 <sup>NS</sup>	16.8 (11.2–23.8) <sup>NS</sup>
Tibolone	113	13.4 (11.2–15.9)	9.8 $\pm$ 7.4 <sup>†</sup>	19.5 (12.6–28.0) <sup>NS</sup>
Parental estrogens	77	9.1 (7.3–11.3)	13.0 $\pm$ 6.8 <sup>NS</sup>	31.2 (21.1–42.7) <sup>NS</sup>
Total	843	100.0	11.5 $\pm$ 6.9	22.5 (19.8–25.5)

Comparisons are made in relation to the vaginal estrogen group\* using the Student's *t*-test for total MRS scores or  $\chi^2$  test for rate of women presenting severe total MRS scores; †, *p* < 0.002  
NS, non-significant

The most important factor related to current HT use was women perceiving HT as 'good' for physical and psychological well-being (OR 11.53; 95% CI 9.41–14.13). Other factors included being postmenopausal, considering that the menopause affects quality of life, having had surgical menopause, being sexually active, having used alternative therapies, and accessing private health care. Obesity was related to lower HT use (OR 0.72; 95% CI 0.57–0.91) (Table 4).

An important number of surveyed women (48.8%) had used HT in the past and abandoned it. Reasons for this behavior are depicted in Table 5; 59.8% of these past users abandoned use due to improvement of menopausal symptoms. Interestingly, current total MRS scores in this latter group were significantly lower ( $9.1 \pm 6.4$ ) when compared to scores found in women reporting other reasons for abandoning HT (range 13.2–16.5). The same trend was observed when MRS scores are expressed as percentage of severity.

Reasons for not using HT among never users are depicted in Table 6. The most frequent reason was that it had not been medically prescribed (28.0%) followed by the lack of menopausal symptoms at the time (27.8%). The latter women currently presented lower total MRS scores as compared to the former ( $7.4 \pm 6.0$  vs.  $13.3 \pm 7.2$ , *p* < 0.0001). Of women who

**Table 4** Factors related to current use of hormone therapy (HT). Logistic regression analysis

Factors	Odds ratio	95% confidence interval
HT perceived as 'good' for physical and psychological well-being	11.53	9.41–14.13
Being postmenopausal	3.47	2.75–4.36
Considers that the menopause affects quality of life	2.54	1.92–3.36
Having had surgical menopause	1.76	1.38–2.24
Sexually active	1.57	1.25–1.96
Having used alternative therapies	1.53	1.22–1.92
Accessing private/paid health-care system	1.50	1.24–1.81
Being obese (body mass index $\geq 30$ kg/m <sup>2</sup> )	0.72	0.57–0.91

had never used HT, 15.0% considered the menopause as a natural process that does not require therapy and 10.9% preferred to treat their menopausal symptoms with alternative therapies. Less frequent reasons for not using HT among never users included fear of cancer, weight gain, costs and others.

Regarding the use of alternative therapies for the treatment of menopausal symptoms, the present study found that 19.5% of women were using this type of therapy (Table 7). Mean total MRS scores among these women were significantly higher as compared to those using HT or non-therapy users ( $13.6 \pm 7.3$  vs.  $11.5 \pm 6.9$  and  $10.9 \pm 7.1$ , respectively, *p* < 0.05). Equally, the rate of women presenting severe MRS total scores (hence more severe menopausal symptoms) was significantly higher among alternative therapy users as compared to HT and non-therapy users (35.1% vs. 22.5% and 22.2%, respectively).

## DISCUSSION

The present study showed that current HT use remains low in Latin America (12.5%), a rate which is slightly lower than the 14.7% found in 2011 in a REDLINC study among Latin America women aged 40–59 years<sup>17</sup>, and yet lower than the 22.6% reported in 2006 in another multinational Latin American study among women of the same age<sup>23</sup>. This observation indicates that, although progress has been made in the interpretation of the results of the WHI study, the net effect is that women continue not to use HT.

In the present study, HT users displayed differences in a number of aspects suggesting socioeconomic differences as compared to never or past HT users. The National Health Survey, conducted by the Ministry of Health of Chile, which is representative of the entire Chilean population, indicates that women who are more educated (a strong marker of socioeconomic status)<sup>24</sup>, weigh less (3 kg less and 3.2 kg/m<sup>2</sup> BMI less), are taller (7 cm greater) and have lower abdominal circumference (9 cm less) than those less educated. HT users in

**Table 5** Reason for abandoning hormone therapy (HT) among past users and current menopausal symptoms for each reason. Data are given as mean  $\pm$  standard deviation or % (95% confidence interval)

Reasons	n	% of women (95% confidence interval)	Menopausal symptoms	
			Total MRS score <sup>†</sup>	Severe total MRS scores <sup>‡</sup>
Menopausal symptoms decreased*	1964	59.8 (58.1–61.4)	9.1 $\pm$ 6.4	14.4 (12.9–16.0)
Unconcerned	352	10.7 (9.7–11.8)	15.2 $\pm$ 6.9 <sup>a</sup>	44.6 (39.4–50.0) <sup>c</sup>
Fear of negative side-effects	318	9.7 (8.7–10.8)	14.8 $\pm$ 6.9 <sup>b</sup>	42.5 (37.0–48.1) <sup>c</sup>
Cost	168	5.1 (4.4–5.9)	14.7 $\pm$ 6.6 <sup>a</sup>	37.5 (30.2–45.3) <sup>c</sup>
Did not tolerate it	166	5.1 (4.3–5.9)	16.5 $\pm$ 7.0 <sup>a</sup>	47.6 (39.8–55.5) <sup>c</sup>
Withdrawal recommended by physician	160	4.9 (4.2–5.7)	13.2 $\pm$ 7.7 <sup>b</sup>	36.3 (28.8–44.2) <sup>c</sup>
Did not improve symptoms	158	4.8 (4.1–5.6)	14.3 $\pm$ 7.0 <sup>a</sup>	38.6 (31.0–46.7) <sup>c</sup>
Total	3286	100.0	11.4 $\pm$ 7.2	25.4 (23.9–26.9)

\*, Reference group for all comparison; <sup>†</sup>, significant *p* values determined with the Student's *t*-test<sup>a</sup> or the Mann-Whitney test<sup>b</sup>; <sup>‡</sup>, significant *p* values determined with the  $\chi^2$  test<sup>c</sup>

our study share all these features suggesting socioeconomic differences related to HT use. Equally, while 55.8% of HT users pay for their medical care, 46.1% of past and 41% of never users do so. This relationship between higher socioeconomic status and greater HT use has been described previously<sup>25</sup>.

Despite the fact that HT is the most effective therapeutic intervention for menopausal symptoms, it was of surprise to find that no significant differences were observed in the intensity of menopausal symptoms among users and non-HT users. We have previously reported that the percentage of women with severe vasomotor symptoms was slightly higher among HT users as compared to non-users (58.6 % vs. 53.8 %, *p* = 0.001) and that this paradox is most likely to be caused by selection bias<sup>17</sup>. For example, in this mentioned study<sup>17</sup>, HT use was more frequent in surgically menopausal women, a group with a higher prevalence of severe menopausal symptoms as compared to non-users (29.2% vs.

12.3%, respectively, *p* < 0.0001). In the same study when only surgically menopausal women are analyzed, HT users had less severe symptoms than non-users (9.0% vs. 16.1%, *p* < 0.0001); logistic regression analysis confirmed symptomatic benefit of HT use.

The present study showed that the prevalence of surgical menopause was higher among HT users as compared to non-users (31.1% vs. 14.1%, *p* < 0.0001); hence without therapy the severity of menopausal symptoms would be higher. HT use attenuated symptoms, displaying similarity with non-HT users. Studies in the United States<sup>26,27</sup>, Brazil<sup>29</sup> and Korea<sup>29</sup> have also found that HT users have more or similar menopausal symptoms than non-users.

Several studies have shown that HT reduces the risk of diabetes mellitus; our data demonstrate the contrary. A possible explanation could be supported by the fact the majority of studies favoring a protective role for HT have been performed on Anglo-Saxon populations that have a different

**Table 6** Reasons for not using hormone therapy (HT) among never users and current menopausal symptoms for each reason. Data are given as mean  $\pm$  standard deviation or % (95% confidence interval)

Reasons	n	% of women (95% confidence interval)	Menopausal symptoms	
			Total MRS score <sup>†</sup>	Severe total MRS scores <sup>‡</sup>
Did not have menopausal symptoms at the time or upon consultation*	724	27.8 (26.1–29.6)	7.4 $\pm$ 6.0	9.8 (7.8–12.3)
HT was not prescribed	729	28.0 (26.3–29.8)	13.3 $\pm$ 7.2 <sup>a</sup>	30.6 (21.0–41.5) <sup>c</sup>
The menopause is a natural process	389	15.0 (13.6–16.4)	12.1 $\pm$ 7.3 <sup>a</sup>	25.7 (21.5–30.4) <sup>c</sup>
Prefers alternative therapies	283	10.9 (9.7–12.2)	14.5 $\pm$ 7.1 <sup>a</sup>	35.3 (29.8–41.2) <sup>c</sup>
Fear of cancer	218	8.4 (7.4–9.5)	14.1 $\pm$ 6.6 <sup>a</sup>	34.4 (28.1–41.1) <sup>c</sup>
Various reasons	137	5.3 (4.5–6.2)	12.1 $\pm$ 6.8 <sup>b</sup>	24.8 (17.8–32.9) <sup>c</sup>
Fear of gaining weight	85	5.0 (4.5–6.2)	13.8 $\pm$ 6.0 <sup>b</sup>	30.6 (27.3–34.1) <sup>c</sup>
Hormones are expensive	37	1.4 (1.0–2.0)	14.3 $\pm$ 6.6 <sup>b</sup>	37.8 (22.5–55.2) <sup>c</sup>
Total	2602	100.0	11.3 $\pm$ 7.3	24.7 (23.1–26.4)

\*, Reference group for all comparison; <sup>†</sup>, significant *p* values determined with the Mann-Whitney test<sup>a</sup> or Student's *t*-test<sup>b</sup>; <sup>‡</sup>, significant *p* values determined with the  $\chi^2$  test<sup>c</sup>

**Table 7** Comparison of menopausal symptoms (intensity and rate of severe MRS scores) in accordance with the type of treatment. Data are given as mean  $\pm$  standard deviation or % (95% confidence interval)

Therapies	n	% of women (95% confidence interval)	Menopausal symptoms	
			Total MRS score <sup>†</sup>	Severe total MRS scores <sup>‡</sup>
Not using therapies for the menopause*	4573	67.9 (66.8–69.1)	10.9 $\pm$ 7.1	22.2 (21.0–23.5)
Alternative therapies ('natural')	1315	19.5 (18.6–20.5)	13.6 $\pm$ 7.3 <sup>a</sup>	35.1 (32.5–37.7) <sup>b</sup>
Currently using hormone therapy	843	12.5 (11.7–13.7)	11.5 $\pm$ 6.9 <sup>a</sup>	22.5 (19.8–25.5) <sup>NS</sup>
Total	6731	100.0	11.5 $\pm$ 7.2	24.8 (23.8–25.8)

\*, Reference group for all comparison; <sup>†</sup>, significant *p* values determined with the Student's *t*-test<sup>a</sup>; <sup>‡</sup>, significant *p* values determined with the  $\chi^2$  test<sup>b</sup>

NS, non-significant

genetic blend when compared to Latin American women. There could be genetic variations in terms of estrogenic receptors determining a different diabetes risk in relation to HT. It is known that polymorphisms of the estrogen receptor may relate to lower adiponectin levels, a factor associated with a higher diabetes risk<sup>30</sup>. Another explanation may rely on the fact that the results of these studies favoring diabetes risk reduction were obtained in the era prior to the WHI trial when estrogen dosages were higher. Interestingly, contraceptives, which have more pronounced metabolic effects as compared to HT, are associated with a lower risk for diabetes<sup>31</sup>.

Current HT users have totally different perceptions regarding the menopause as compared to never users, demonstrating that perceptions may influence the decision of whether to use HT. Indeed, current HT users think more often that the menopause affects female physical and psychological well-being (90.2% vs. 71.4%, *p* < 0.01), that there are treatments for menopausal symptoms (91.2% vs. 68.0%, *p* < 0.01), that treatment consists of HT (88.8% vs. 46.8%, *p* < 0.01) and that HT is 'good' (79.8% vs. 24.6%, *p* < 0.01). Past HT users have perceptions of HT that are similar to never users. These results emphasize that women need to have information regarding the effects of the menopause and HT. The importance of awareness and knowledge are shown by a study that found that women who are 'more informed' are more likely to use HT<sup>32</sup>. The same trend can be observed in another study showing that the majority of German gynecologists who answered the survey (response rate 33.7%) favor HT use for themselves or their spouses (female gynecologists, 96%; male gynecologists, 98.5%)<sup>33</sup>. Our study shows that considering HT as 'good' is the main factor related to its use (OR 11.53, 95% CI 9.41–14.13), surpassing even being postmenopausal (OR 3.47, 95% CI 2.75–4.36). However, study design did not allow the assessment of the severity of menopausal symptoms before HT initiation, which should be the main factor related to its use.

Since the WHI study, there is concern regarding thrombotic risk in relation to oral HT. However, our study shows that oral therapy continues to be the main route of HT administration in many Latin American countries. As in the USA, for

decades the oral route in Latin America has been the predominant one; nevertheless, transdermal HT has occupied a dominant prescribing position in Europe due its metabolic advantages<sup>34</sup>. Overall, we did not observe differences in the intensity of symptoms in relation to the several HT options. Moreover, if we compare the severity of menopausal symptoms in oral HT users with that observed among users of vaginal estrogen (which only improves genitourinary symptoms), no significant differences were found and this could be because the indication for vaginal topical therapy is vaginal atrophy with little or no other menopausal symptoms<sup>35</sup>.

Nearly half of surveyed women (48.4%) had used HT in the past and subsequently abandoned it. In 59.8%, the main reason was the disappearance of menopausal symptoms, followed by being unconcerned about the fact (10.7%). A third reason included the fear of the negative effects related to HT (9.7%). Comparison of our results with other studies is difficult due to the variability of applied protocols. For instance, in Finland, the main reasons for abandoning HT include: the desire to be free of medication, side-effects, reactions to media advertising and fear of cancer<sup>36</sup>. Another study, carried out in Italy, reported side-effects and fear of breast cancer as the main causes for HT discontinuation<sup>37</sup>. In our study, side-effects ('does not tolerate HT') as a reason for discontinuation was given by only 5.1% of women. This is interesting because many women in our study access free state health centers and the economic cost of HT is not mentioned as a reason for abandoning the therapy. In our study, medical recommendation was another reported reason for abandoning treatment in almost 5% of surveyed women. The same reason for abandoning HT was reported by 50% of Turkish women<sup>38</sup>. As already mentioned, the main reason for abandoning HT in our study was the disappearance of symptoms. It is noteworthy, however, that 14.4% of these women had total MRS scores considered as severe, a rate that is lower than the 40% reported by those who gave other reasons.

Lack of medical prescription (28%) and the absence of menopausal symptoms (27.8%) were main reasons among never users for not using HT. Highlighting this was the fact of finding lower MRS scores and a lower rate of symptom

severity among never users. However, total MRS scores and rate of severity were higher among women whose doctors did not prescribe HT. In agreement with our results, one study showed that the main reported reason for not using HT is the non-indication by their doctors (56.6%) and that only 8.3% of them were concerned about side-effects<sup>39</sup>. The fear of cancer and weight gain were only reported by 8.4% and 5.0% of women, respectively, in our study. Emphasizing the importance of the physician in the indication of HT, one study (9785 women, response rate 19.3%) found that about 44% of German women chose to use HT after being advised by their gynecologists. This percentage dropped to 14.3% and 11.3% if the advice came from friends or the media, respectively, and 64.9% of them considered breast cancer as the main risk related to the use of HT, followed by weight gain (53.4%) and thromboembolism (48.0%)<sup>32</sup>.

In our study, 19.5% of women ( $n = 1315/6731$ ) used alternative 'natural' therapies. This group displayed higher total MRS scores as compared with current HT users or those not using any therapy for the menopause. Moreover, 35% of these women displayed severe menopausal symptoms as opposed to 22.5% among HT users and 22.2% in those not using any therapy. These data are consistent with studies pointing out the poor performance of these alternative therapies<sup>40</sup>.

Finally, regarding the limitations of the present study, one should mention that, due to the heterogeneity of Latin American health-care systems, income and quality of governmental health-care recommendations, the overall results of the present study may not be totally applicable to any particular site. In subsequent publications, we will perform a more detailed sub-analysis of our data.

We may conclude that, despite knowing the limitations of the WHI study, HT use for menopausal symptoms in many countries has not regained the levels observed a decade ago and continues to be low. The main factors related to HT use

included positive perceptions about HT, being postmenopausal or surgically menopausal, and presenting a number of features related to better socioeconomic status. Almost half of surveyed women had used HT in the past and abandoned it, mainly due to improvement of menopausal symptoms or being unconcerned about the fact; fear of cancer or other side-effects was reported by less than 10% of women. Reasons for never HT use included lack of medical indication, followed by the absence of menopausal symptoms. Finally, users of natural alternative therapies displayed a high prevalence of severe menopausal symptoms.

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