# Latin American position on the current status of hormone therapy during the menopausal transition and thereafter☆

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**Abstract**

*Objective:* Data from placebo-controlled, randomized clinical trials conducted during the past few years resulted in critical re-evaluation of the overall health benefits of hormone therapy (HT) in women during the menopausal transition and thereafter. These data stimulated vigorous debate among experts and produced several position papers by North American and European authorities providing guidance on the use of HT. It is well known that cultural, geographic and ethnic differences influence the acceptance and risk perception of HT. Therefore, it was considered essential to present a position specifically relevant to Latin American countries.

*Methods:* A Latin American Expert Panel, convening in Salvador, Bahia, Brazil, obtained consensus on recommendations for HT that incorporated the findings of the most recently published reports. The panelists' opinions were surveyed by means of the Likert scale along five categories ranging from complete agreement to complete disagreement.

*Results:* The Panel presented 13 recommendations and considered three additional issues relevant to HT use. There was consensus that HT during the perimenopause and thereafter is warranted in Latin American women in particular for the management of vasomotor symptoms. HT may also be an option for osteoporosis prevention in women at significant risk, after evaluation of risks/benefits and after consideration of alternative therapies. HT should be individualized and prescribed at the lowest effective dose.

*Conclusions:* The Panel concluded that HT remains a safe and effective treatment option for peri- and postmenopausal Latin American women.

*Keywords:* Position statement; Hormone therapy; Latin America; Menopause; Consensus; WHI study

☆ Affiliation of Panel members are given in Appendix A.

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## 1. Introduction

Cultural, geographic and ethnic differences make acceptance and risk perception of hormone therapy (HT) different in various regions of the world, thus making it advisable to achieve regional consensus that will be in conformity with the realities of each specific region.

In the past several years, new findings from clinical studies have led to a critical re-evaluation of the overall health benefits of HT in women during the menopausal transition period and thereafter. This development was principally triggered by results from placebo-controlled, randomized clinical trials, such as the Heart and Estrogen/progestin Replacement Study (HERS), the Estrogen Replacement and Atherosclerosis Study (ERAS) and the Women's Health Initiative (WHI) study, as well as the findings of the observational Million Women Study (MWS), among others. Government health authorities, academic specialists, representatives of medical associations and other expert panels have reevaluated the safety of HT in light of the new findings in order to provide guidance to health practitioners, to actual or potential HT users and to the lay public in general.

An expert panel of Latin American specialists in women's health care met on October 1–3, 2004, in Salvador, Bahia, Brazil, to discuss the current status of postmenopausal HT in light of the most recent published reports and as relevant to the region. The panelists originated from: Argentina, Brazil, Chile, Colombia, Mexico and Venezuela. Prior to this meeting, they had collaborated on the same subject as experts at consensus meetings in their country of origin or at regional meetings. The goal of the present meeting was to consolidate the different positions of previous meetings and to strengthen the recommendations drawn up by health specialists in Latin America who had participated in national or regional activities (consensus meetings) on HT and the menopause. A second, equally important objective was to develop a uniform Latin American position statement containing simple, accurate and solid recommendations for HT used by women of Latin American descent. The information in this document is intended to dissipate the uncertainty, doubts and fears often expressed by health care providers and by current or future users of HT in the Latin American region.

## 2. Terminology

### 2.1. Recommendation

A recommendation was defined as: based on current scientific evidence with respect to hormone therapy, to suggest or counsel something worthy and pertinent of being counseled to health professionals to enable them to make decisions during the practice of their duties.

### 2.2. Consideration

A consideration was defined as something about which thought should be given before a decision related to HT was made, in agreement with current medical evidence.

### 2.3. Hormone therapy

The following terminology was applied to postmenopausal hormone therapy (HT): estrogen therapy or unopposed estrogen therapy both refer to regimens using only estrogen and are abbreviated ET. Regimens combining estrogen plus progestogen are abbreviated EPT. The term progestogen includes both progesterone and synthetic progestational agents. The latter are referred to as progestins [1]. The term HT is applied to the administration of hormones (ET or EPT) irrespective of dose, route of administration or type of preparation (salt form, vehicle or excipient) or the presence of menopausal symptoms in the woman.

## 3. Background information

In their development of guidelines for the use of HT, the Panel focused on the major areas affected by the recent findings, i.e., cardioprotection, breast cancer, cognition, dementia and venous thromboembolism. The Panel also took into consideration the proven benefits of HT. The following section summarizes published information evaluated by the Panel in order to create evidence-based recommendations for HT during the menopausal transition and thereafter.

### 3.1. Cardiovascular disease

Prior to the recent findings, the great majority of observational studies suggested a substantial

cardioprotective effect of ET [2]. This conclusion was based on information from population-based or community-based case-control studies or prospective cohort studies. While less information was available on the effects of adding progestogen, it was generally believed that the addition of progestational agents did not appear to attenuate the cardioprotective effects of ET [3]. The evidence that estrogen protects against heart disease was considered quite strong, and it was believed that the largest benefits of both estrogen and estrogen plus progestin would be for women with the greatest risk of heart disease [2].

Results from several well-controlled prospective studies subsequently challenged the tenet that HT protects against heart disease. As expected, the new data stimulated vigorous debates among experts and resulted in the publication of several position papers by North American and European authorities to provide guidelines for HT use [1,4–6].

A statement on HT use has been published in Spanish under the auspices of the Latin American Federation of Climacteric and Menopause Societies (FLASCYM) [7].

The revised guidelines reflected to a large extent the results from two secondary prevention studies (HERS and ERAS) and one large primary prevention study (WHI).

HERS was a randomized, blinded, placebo-controlled study of 2763 postmenopausal women (mean age = 66.7 years) conducted with the objective of determining whether estrogen plus progestin therapy alters the risk for coronary heart disease (CHD) in women with established coronary disease [8]. Women received one tablet daily of 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo. The average follow-up period was 4.1 years with an additional follow-up of 2321 women for 2.7 years (HERS II) during which the women received open-label HT at personal physicians' discretion [9]. Overall, there were no statistically significant differences between groups after 4.1 years of follow-up, but a statistically significant time-trend was observed, with more CHD events in the hormone group in year 1 and fewer events in years 4 and 5. Higher rates of thromboembolic events and gallbladder disease were observed in the hormone group. HERS II found no significant decreases in CHD during the follow-up period and concluded that after 6.8 years, HT did not reduce risk of cardiovascular events in women with CHD [9].

ERAS evaluated 309 postmenopausal women (mean age 65.8 years) with angiographically verified coronary disease. The mean follow-up period was 3.2 years. Participants were randomized to one of three groups treated daily with 0.625 mg CEE, 0.625 mg CEE + 2.5 mg MPA, or placebo. The data indicated that neither estrogen alone nor estrogen plus progestin affected the progression of coronary atherosclerosis in women with established disease [10].

The above studies found that conjugated equine estrogens with or without added progestogen failed to slow the progression of CHD. A double-blind study of 226 postmenopausal women (mean age 63.5 years), who had at least one coronary artery lesion, investigated whether the endogenous estrogen 17β-estradiol (E2) could effectively slow the progression of established atherosclerosis [11]. The women were randomized to daily oral therapy with 1 mg E2 alone, daily E2 (1 mg) plus 12 consecutive days adjunctive MPA every month, or placebo. Coronary artery stenosis was measured by quantitative coronary angiography. After a median follow-up of 3.3 years, results revealed that neither E2 alone or in sequential combination with MPA significantly affected the progression of atherosclerosis [11].

The WHI study (planned duration = 8.5 years) was a large, prospective, randomized, controlled primary prevention trial. The EPT component of WHI was conducted in 16,608 postmenopausal women with an intact uterus, aged 50–79 (mean age 63.2) years. Women were randomly assigned to placebo ($n = 8102$) or therapy ($n = 8506$) consisting of daily 0.625 mg CEE plus 2.5 mg MPA. The primary outcome was CHD (non-fatal myocardial infarction or CHD death) with invasive breast cancer as the primary adverse outcome. The EPT component of WHI was stopped early, after a mean follow-up period of 5.2 years, based on health risks that exceeded health benefits [12].

In contrast to the earlier data from observational studies, WHI detected no cardioprotective effect following EPT. The observed overall CHD rates were low and most of the excess relative to placebo represented non-fatal myocardial infarctions [12]. The WHI data suggested that EPT might increase the risk of CHD, particularly during the first year after initiation of therapy. It was therefore concluded that EPT should not be prescribed for the prevention of cardiovascular dis-

ease [13]. However, there are important age differences between the participants in the observational studies and those in the clinical trials at the time of initiation of treatment and this may have affected the outcome.

The estrogen-alone component of WHI recruited 10739 postmenopausal women aged 50–79 years who had undergone prior hysterectomy. The study participants were randomly assigned to receive either placebo ($n = 5429$) or 0.625 mg CEE ($n = 5310$) daily. The primary outcome was CHD (non-fatal MI or CHD death). After an average 6.8 years of follow-up it was concluded that estrogen alone does not affect the risk of heart disease in postmenopausal women with prior hysterectomy [14]. However, there was a trend towards fewer cardiovascular events when hormone therapy was initiated at a younger age [14]. This trend has recently been confirmed in a report of final, centrally adjudicated results for the primary efficacy outcome (myocardial infarction or coronary death) and secondary outcomes. The authors concluded that there was a suggestion of lower coronary heart disease risk with CEE among women 50–59 years of age at baseline [15].

It is noteworthy that most of the randomized clinical trials, such as WHI and HERS, were conducted in women who were much older than those for whom hormones are usually prescribed and therefore extrapolation of the results obtained in the clinical trials has to be made cautiously.

### 3.2. Venous thromboembolism

Consistent with several earlier reports [16], both HERS [8] and the WHI study [12] reported increased HT-related risks of venous thromboembolism.

### 3.3. Stroke

Data from the WHI study indicate an increased risk of stroke in generally healthy postmenopausal women following HT. The risk was significant both with combined CEE/MPA therapy [17] and with CEE—only therapy [14]. The increased risk in the CEE/MPA group applied to ischemic, but not to hemorrhagic stroke. In contrast, HERS found no significant effect on the risk for stroke following HT with CEE/MPA in postmenopausal women with established coronary disease [18].

### 3.4. Breast cancer

Fear of breast cancer is an essential reason for women to shun HT and a major factor for discontinuing therapy [19]. Prior to WHI and MWS, a large number of studies had investigated the risk of breast cancer in relation to HT. In 1997, the collaborative group on hormonal factors in breast cancer reanalyzed about 90% of the worldwide epidemiologic evidence relating HT to breast cancer risk [20]. Data from 52,705 women with breast cancer and 108,411 women without breast cancer were reanalyzed in that study.

The group concluded that the relative risk of having breast cancer diagnosed increased by a factor of 1.023 for each year of use in current users or in women who had used HT 1–4 years prior to diagnosis. The relative risk was 1.35 for women who had used HT for 5 years or longer. The risk was reduced after cessation of HT and largely disappeared after about 5 years. No marked differences were found between different types and doses of hormones or between regimens of estrogen alone and in combination with progestogen [20].

The MWS surveyed 1,084,110 women, aged 50–64 years, in the United Kingdom. About half of the women had used HT. The study found that current users of HT were more likely to develop breast cancer and to die from it than were never users, but past users were not at an increased risk of incident or fatal disease. The increased risk was apparent with use of preparations containing estrogen only, estrogen plus progestogen, as well as tibolone. The magnitude of the associated risk was substantially greater for estrogen–progestogen combinations than it was for other types of HT [21].

The estrogen–progestin component of the WHI study revealed a greater risk of breast cancer in the estrogen plus progestin group compared with placebo. The invasive breast cancers diagnosed in both groups were similar in histology and grade, but were larger and at a more advanced stage in the HT group. After 1 year the percentage of women with abnormal mammograms was substantially higher in the HT group, and this pattern continued during the study duration. The investigators concluded that estrogen plus progestin may stimulate breast cancer growth and/or hinder breast cancer diagnosis by increasing breast density [22].

Contrasting with the results following estrogen plus progestin therapy, the data from the WHI estrogen-alone component revealed no increased risk in breast

cancer during an average follow-up period of 6.8 years. On the contrary, the breast cancer rate was 23% lower in the CEE group than in the placebo group, an effect that barely missed statistical significance [14].

### 3.5. Cognition/dementia

Prior to the Women's Health Initiative Memory Study (WHIMS), a number of observational studies suggested that HT decreases the incidence or delays the onset of dementia, primarily of Alzheimer's disease [23]. WHIMS was an ancillary nested trial within WHI. A total of 4532 women were recruited from the CEE/MPA-placebo component and 2947 women from the CEE-placebo component of WHI. The women were 65–79 years old. In each group, approximately one half of the women received HT and one half placebo [24]. Results from the WHIMS indicated that CEE/MPA increased the risk of probable dementia in women aged 65 years or older and did not prevent mild cognitive impairment (MCI) [25]. A small increased risk of clinically meaningful cognitive decline was observed in the estrogen plus progestin group [26]. Estrogen therapy alone did not reduce dementia or MCI and increased the risk for both end points combined. The risk for each end point increased when pooled data for estrogen-alone and estrogen plus progestin were analyzed. As a result, use of HT to prevent dementia of cognitive decline in women 65 years of age or older was not recommended [24]. However, a limitation of this study relates to the age of the population when HT was initiated, making it difficult to extrapolate these results to women who initiate HT during the menopausal transition.

### 3.6. Benefits of HT

The efficacy of HT (ET/EPT) in the treatment of vasomotor and urogenital symptoms has been firmly established [27,28]. Similarly, the benefits of HT in the prevention of osteoporosis and in decreasing fracture risk have been documented in numerous studies. A meta-analysis completed in 2002 [29] concluded that HT had a consistent beneficial effect on bone mineral density (BMD), the major predictor of fracture risk in postmenopausal women [30], and that it was associated with a trend toward reduced incidence of vertebral and non-vertebral fractures [29]. Importantly, significant beneficial effects on spine and hip BMD were observed at lower than commonly prescribed doses of CEE, e.g., 0.3 mg/day, with or without MPA [31], and with ultralow-dose of transdermal estradiol (0.014 mg/day [32].

The WHI study demonstrated in a large clinical trial setting that postmenopausal estrogen/progestin therapy significantly reduces the incidence of hip, vertebral and other osteoporotic fractures. Specifically, HT (0.625 mg/day CEE plus 2.5 mg/day MPA) for a mean follow-up period of 5.2 years significantly reduced the relative hazard for hip fractures by one third (hazard ratio [HR], 0.66; 95% nominal confidence interval [nCI], 0.45–0.98) and of vertebral fractures by one third (HR, 0.66; 95% nCI, 0.44–0.98). Significant reductions in relative hazards for other osteoporotic fractures by 23% (HR, 0.77; 95% nCI, 0.69–0.86) and total fractures by 24% (HR, 0.76; 95% nCI, 0.69–0.85) were also observed. Colorectal cancer rates were reduced by 37% (HR, 0.63; 95% nCI, 0.43–0.92) [12].

### 3.7. Non-hormonal prescription options

The Panel also evaluated non-hormonal therapy options, used alone or in combination with HT. These options included use of antidepressants such as venlafaxine, paroxetine or fluoxetine, anticonvulsants, such as gabapentin and antihypertensives such a clonidine, and alpha and beta blockers [33–36].

## 4. Methodology

The present panel of 14 members was chosen from 110 experts who had attended one or more of three consensus meetings held in a Latin American country in the past 3 years. Two of these meetings, one held in Brazil the other in Mexico, were national consensus meetings, and one, held in Argentina, was a Latin American regional consensus meeting. These meetings employed extensive search strategies and used criteria of evidence-based medicine (summarized in the preceding Section 3) as a basis to achieve consensus on HT. The formal documents originating from these meetings included a published article [37], a book [38] and meeting minutes [39].

An instrument based on the common conclusions of these documents was drawn up for validation by the present panel. The instrument consisted of 13 com-

mon recommendations and 4 considerations. The Likert scale was used in the validation process. The scale requires the individual to agree or disagree with a statement along five categories, ranging from "complete agreement" to "complete disagreement" [40]. A conclusion listed in the instrument was considered to have been validated for inclusion in the present position statement when 80% of the panelists were in complete agreement or agreed more than they disagreed. A conclusion was considered invalid and rejected when 80% disagreed completely or disagreed more than they agreed.

## 5. Results

Of the 13 recommendations contained in the instrument, the panelists accepted three without change. Four recommendations received the agreement of all panelists but a suggestion for an alteration to the text was implemented. A further four recommendations were validated with the agreement of 90% of the panelists and two recommendations received partial agreement of 85% of the panelists. All 13 common recommendations were therefore validated for inclusion in the position statement. The Panel added one conclusion, considered relevant, which was not listed in the original instrument. Two of the four considerations contained in the instrument were validated unanimously and one was validated at 92%. One consideration was eliminated because the Panel felt that there was insufficient evidence to support it.

## 6. Recommendations

1. Hormone therapy (HT), consisting either of estrogen-only therapy (ET) or combined estrogen plus progestogen therapy (EPT), is recommended as the principal and most important option for the treatment of symptoms (vasomotor symptoms, urogenital complaints) during the menopausal transition and shortly thereafter. In some cases, after thorough evaluation, HT may also be considered to control irregular vaginal bleeding, especially during the transition to menopause.
2. The primary reason for adjunctive progestogen is the protection of the endometrium from unopposed estrogen. Postmenopausal women without a uterus should not be prescribed a progestogen. In some cases, progestogen therapy may also be considered in women without a uterus who suffer from endometriosis.
3. Hormone therapy may be an option for the prevention of osteoporosis in women at significant risk of osteoporosis, provided the risks and benefits have been evaluated and alternate therapies have been considered and found to be less efficacious or contraindicated. Hormone therapy is not recommended in older women exclusively for the prevention or treatment of osteoporosis.
4. The lowest effective dose consistent with treatment goals should be used.
5. Hormone therapy should be given for as long as the benefits outweigh the risks. Risks/benefits should be periodically evaluated, particularly if a woman is receiving a progestin.
6. The dose and schedule of HT should be individualized and take into account the clinical state of a woman, her age, the time of her menopausal transition and the various symptoms.
7. Promotion of a healthy lifestyle is recommended as part of the integrated medical management of symptomatic women in the menopausal transition and thereafter. This should include daily physical activity, a healthy, balanced diet, including appropriate caloric intake, and a body mass index (BMI) of 20–25 $kg/m^2$. A woman should be encouraged to suspend habits known to be harmful to health, such as a sedentary lifestyle, smoking or excessive alcohol consumption.
8. Since HT is associated with a slight increase in risk of developing venous thromboembolism, risk factors should be identified and evaluated, including a woman's medical history.
9. Hormone therapy is not indicated exclusively for the primary or secondary prevention of cardiovascular disease.
10. Hormone therapy should not be used exclusively for the treatment of cognitive impairment, Alzheimer's disease or other forms of dementia.
11. Hormone therapy is not recommended exclusively for the prevention of colon cancer.
12. Prior to HT a woman must be informed about the risks and benefits of HT, its potential general side effects, and side effects that may apply specifically

to her situation. This should be repeated at each of her periodically scheduled follow-up visits during treatment.

13. Each woman has the right to participate in the decision-making process with respect to HT. To do so, she should have received appropriate general information and information regarding her specific situation.

## 7. Considerations

In evaluating HT as a treatment option the following points should be considered in agreement with current medical evidence:

1. No increase in breast cancer risk has been observed in the first 7 years of therapy with estrogen alone. Therapy with estrogen plus progestin may lead to a slight increase in risk.
2. Addition of other medications to HT, such as antidepressives, anxiolytics and diet supplements, is not contraindicated in cases when these agents are considered appropriate adjuncts for the management of menopausal symptoms during the menopausal transition and thereafter.
3. Addition to HT of medication for the prevention or treatment of coexisting ailments during the menopausal transition, such as platelet aggregation inhibitors, statins and angiotensin-converting enzyme inhibitors is not contraindicated.

## 8. Conclusion

After evaluating the current state-of-the-arts knowledge together with earlier information, the Panel concluded that the use of HT during the perimenopause and thereafter is warranted in Latin American women. The Panel considered HT the gold standard for the management of moderate to severe vasomotor symptoms associated with the menopause. Hormone therapy should be prescribed at the lowest effective dose and should be used only in those symptomatic women in whom its benefits outweigh its risks. Hormone therapy should be given in an individualized manner for each woman after evaluating the risk/benefit ratio associated with its use. It should be emphasized that despite the controversial and contradictory information resulting from observational and placebo-controlled randomized studies, HT continues to be a safe treatment option.

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Prof. Espinosa Larrañaga was the facilitator of the consensus meeting. He was not one of the panel members.

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* These members acted as scientific advisors. They did not participate in the panel meeting but reviewed and signed the position statement after its acceptance by the Panel.

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