Menopausal hormone therapy: back in the ring

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"As for science, you can not do anything but grow"

Galileo Galilei

Menopausal hormone therapy (MHT), in its almost bipolar essence, has been sanctified and demonized over the years. Since 1942, when conjugated equine estrogens (CEE) were introduced into the market, MHT was considered the source of eternal youth: all women used it in the hope of staying young forever. After the publication of some studies that questioned the safety of estrogens, especially when used without opposition to progestogens, and in 2002, with the results of the Women's Health Initiative (WHI) study, it was considered that MHT increased the risk of cardiovascular diseases and breast cancer, as already stated in a previous article in this portal[1]. As it happens with the indiscriminate use of any therapy, after the publication of the WHI, whose conclusions, with many methodological biases, distorted the benefits of this hormonal therapy. From that moment, the MHT was considered harmful, even carcinogenic, in the treatment of women during menopause.

Motivated to these findings, the prescription of this therapy suffered such a drastic decrease that neither doctors dared to indicate it, nor patients to use it for fear of serious side effects such as breast cancer, stroke, heart attacks, among others. Women during the menopausal transition were condemned to suffer the full range of symptoms associated with that condition and not be able to have the short and long term benefits offered by the MHT. Even young women with

premature ovarian failure, who have a formal indication for hormone therapy, were reluctant to be treated.

There have been several analyzes of the WHI that have been made since 2002 at this time, as well as the follow-up of the patients included in the trials, which have been gradually claiming the role of the MHT. The last of these analyzes is published in JAMA in October 2017 by Mason et al [2]. This report includes a follow-up of 18 years, the longest period recorded in a study of this type, analyzing the general and cause-specific mortality of the two modalities of the WHI study, according to the MHT used: 16,608 patients who received CEE with medroxyprogesterone acetate (CEE + MPA) and 10,739 hysterectomized patients who received CEE alone.

The follow-up of the patients included in both studies was carried out until December 31, 2014. All-cause mortality, cardiovascular mortality, divided into mortality due to coronary heart disease, stroke and other cardiovascular causes, was evaluated. Cancer mortality was also evaluated, subdivided into breast cancer, colorectal cancer and other types, as well as mortality due to the main causes in women such as Alzheimer's disease and other dementias, chronic obstructive pulmonary disease, accidents and others. An analysis was also made by 10-year age groups.

The studies were evaluated during the intervention period, 5.6 years in the case of CEE + MPA and 7.2 years in the CEE alone, with a post-intervention period, that is, once the THM was suspended, and a global follow-up period of 18 years for both trials.

The results were as follows:

1. **All-cause mortality**: there were no differences during the 18 years of follow-up between hormone therapy and placebo, 27.1% vs 27.6% (HR: 0.99, 95% CI 0.94-1.03, P = 0.6). Neither when comparing CEE + MPA and placebo, 26.4% vs. 26% (HR: 1.02, 95% CI 0.88-1.01, P = 0.51), nor CEE and placebo, 28.3% vs. 30%. % (HR: 0.94, 95% CI 0.88-1.01, P = 0.11). There were no differences during the intervention phase (4% hormonal therapy vs 4% placebo), nor in the postintervention, with a HR: 1.04 for CEE + MPA patients and HR: 0.92 for CEE alone. There was an upward trend of HR statistically not significant in the analysis by age: from 50 to 59 years HR: 0.69, from 60 to 69 years HR: 1.04 and from 70 to 79 years HR: 1.13 in the intervention phase.
2. **Cardiovascular mortality:** there were no differences between the hormonal group, alone or combined, and placebo (HR: 1) with respect to stroke or coronary heart disease mortality. There was no difference either when comparing the different treatments in the intervention phase or in the post-intervention phase, or in the analysis stratified by age.
3. **Cancer mortality:** the cancer mortality rate throughout the follow-up was similar between the hormone treatment group and the placebo group (HR: 1.03) and between the two treatment groups (CEE + MPA HR: 1.06 and CEE HR: 0,99). With respect to breast cancer mortality, the HR of the CEE + MPA group was 1.44 (95% CI, 0.97-2.15, P = 0.07) and CEE alone 0.55. Mortality from colon cancer and other types of cancer did not obtain a

statistically significant difference. During the intervention phase, there was no difference with respect to breast cancer mortality in the two treatment groups (HR: 1.1 vs HR: 0.96), but in the post-intervention phase there was a discrete difference between CEE + MPA and CEE alone (HR: 1.08 vs HR: 0.45, respectively). In the age group analysis, there was a non-significant increased HR trend, with a value of 0.74 from 50 to 59 years, 1 from 60 to 69 years to 1.24 from 70 to 79 years. In this last age group, the HR for colon cancer was found to be statistically significantly elevated in the CSE group alone (HR: 2.13, p = 0.03).

4. **Other mortality:** There were no differences between the hormonal group and placebo, however, the deaths from Alzheimer's and other dementias were lower in the hormonal group (HR: 0.85, 95% CI 0.74-0.98 p = 0.03). During the intervention phase there were fewer deaths from other causes in the CEE + MPA group compared with placebo (HR: 0.59). There were no differences in the CEE alone group. During the post-intervention phase, there were fewer deaths due to dementia, especially in the CEE alone group (HR: 0.73). In the analysis by age, there were no significant differences between the groups with respect to the HRs described.

The most important conclusion of this new publication of the WHI is that hormone replacement therapy, EEC + AMP or EEC only used for 5 to 7 years, is not associated with an increase of mortality from all causes, nor during the phase of intervention or after the suspension of treatment. Although this study only evaluated one type of hormonal treatment, with only one route of administration, the two most important conclusions would be that the use of MHT does not increase the risk of death in patients who do not have any formal contraindication to its use, and Hormone therapy does not prevent death for any specific cause. With respect to breast cancer, the increased risk during 18 years follow-up, did not reach a significant statistical difference and is limited to the post-intervention phase in the group of patients between 70 and 79, in this same group in patients with estrogen alone a significant increase in the risk of colon cancer was noted. It is important to clarify that this age group does not currently have any indication of hormonal therapy, because they have overcome the window of opportunity for treatment, which is considered up to ten years after the onset of menopause.

This study brings back to the discussion which are the precise indications of hormone therapy in menopause. Its use should be limited to the treatment of symptoms associated with hypoestrogenism in order to improve the patient's quality of life. It should not be indicated for the prevention of cardiovascular diseases, as it was originally proclaimed, but its use should not be avoided either because it is not related to an increase in mortality, as proposed by different societies, such as the International Menopause Society (IMS)[3] and the North American Menopause Society (NAMS) [4] in their latest recommendations. Taking into account the differences with respect to other MHTs and the different administration routes, in general, the conclusions of this study will allow doctors to prescribe the treatment without fear of increasing the risk of death in the patient who needs it.

Currently, women can spend half of their lives in menopause and THM can facilitate this transition, in conjunction with adjustments in lifestyle such as healthy nutrition and the incorporation of exercise routines. It is important to give us the task of publicly acknowledge the benefits and limitations of hormone therapy in order to use it as indicated to improve the quality of life of women. Beyond the myths, hormone therapy once again has a prominent place in the treatment of climacteric symptoms without the fear of deleterious effects in women.

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