

Should hormone therapy be terminated by age 65 years?

Prior to the publication of the prematurely terminated Estrogen and Progestin (EP) arm of the WHI trial in 2002, hormone therapy (HT) in postmenopausal women was not very complicated. Available evidence from observational studies suggested that the majority of postmenopausal women would benefit from what was then termed hormone replacement therapy (HRT). Besides relief of menopausal symptoms and prevention of osteoporosis, it was widely believed that postmenopausal women using HRT also enjoyed significant protection against coronary heart disease (CHD); hence HRT was easily prescribed without much deliberation. The first WHI study¹ results published in 2002 failed to show this benefit in the population it studied. These findings as well as the increased relative risk for the development of breast cancer received extensive coverage in the media, and it wasn't long before HRT was regarded as being dangerous. The HERS II study² was published in the same month and concluded that HT should not be used to reduce risk for CHD events in women with CHD.

Many women using hormone therapy became concerned and decided to stop taking the medication they were using. Health care providers prescribing HT were suddenly outside their comfort zone as far as prescribing these drugs were concerned. In the months following the WHI publication prescriptions for HT declined significantly. In the USA and Canada there was a decline of 66% (Estrogen/Progestin combination) and 33% for Estrogen alone.³⁻⁵ South African data showed a less dramatic decline of about 15% in private sector sales of HT.⁶ In one study⁷, almost a third of women surveyed stopped their combination HT within six months after the publication of the EP arm of the WHI. The Estrogen alone arm of the WHI⁸ was published in 2004, reporting no adverse effect on CHD and a non-significantly lower risk of breast cancer, but a slight increase in the risk of developing a stroke.

The consensus shortly after the publication of the WHI findings was that HT should be prescribed to postmenopausal women mainly for symptomatic relief of menopausal symptoms. It was then widely advocated to use the lowest dosage for the shortest period of time. It also became evident that symptomatic younger women were the group most likely to benefit from HT, (including CHD prevention) and women more than 10 years after menopause were more likely not to benefit from HT.⁹ Breast cancer risk becomes important after 4 to 5 years of opposed HT.¹

Although there is not much data available on optimal duration of HT, as well as on when and how to stop HT, most

experts agree that short-term use (between 3 and 5 years) of HT in women without contra-indications is safe in symptomatic peri- and postmenopausal women. Seventy nine percent of peri-menopausal and 65% of postmenopausal women do experience vasomotor symptoms with varying frequency. A significant number will have severe symptoms.¹⁰ Untreated women when followed up long enough will report vasomotor symptoms for more than 5 years and 10% of them will experience symptoms for up to 12 years.¹¹⁻¹³ More than half of the women with vasomotor symptoms at randomization to the EP arm of the WHI study still reported symptoms after discontinuing their active tablets.¹⁴ It is therefore difficult to know how long HT will be needed in the women it is prescribed for.

To determine the duration of HT, users it will have to periodically discontinue treatment to find out if symptoms have resolved or not. Women using HT for relief of symptoms are more likely to experience symptoms after cessation of treatment compared to those who used it for prophylactic indications.¹⁴ Gradual discontinuation by either skipping progressively more days between doses or lowering doses every 4 to 6 weeks is not associated with a decrease in the reappearance of climacteric symptoms when compared to abrupt cessation.¹⁵

Having women on HT to periodically cease treatment to assess the presence or not of menopausal symptoms will result in the identification of a large percentage of women who would not require further treatment. However, there will remain a small but significant proportion of women who will require long-term use of HT for symptomatic relief. HT remains the most effective therapy for the relief of menopausal symptoms, specifically night sweats and hot flashes.¹⁶

The concern of long term HT is the increase in the relative risk of developing breast cancer when using the EP combination. After the first 4 to 5 years of use, breast cancer risk increases by 2.3% for every year of use.¹⁷ Breast cancer incidence in the USA also declined with the dramatic drop in HT prescriptions in the year following the publication of the WHI results.³ The increased risk disappears 5 years after cessation of HT. Absolute risk in women starting HT at age 50 and using it for 5, 10 and 15 years respectively are estimated to be 2, 6 and 12 extra cases per 1000 women¹⁷, while the WHI reported 8 extra cases per 10 000 users after 5.2 years. A lower risk for breast cancer was reported in the Estrogen only arm of the WHI study compared to placebo. There is no real evidence of an increased breast cancer risk in long-term use of Estrogen only HT.¹⁸ The updated results of the Estrogen arm of the WHI showed a statistically significant decrease in breast cancer risk in the group of patients who continued their use of unopposed Estrogen.¹⁹ This conflicting effect of HT on breast cancer risk is difficult to explain, possible

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mechanism include adverse affects of progestogens, whether postmenopausal HT initiates the growth of new breast cancer, or if the epidemiologic data reflect an impact on preexisting tumors.²⁰

Long term or extended HT use in a woman where it is indicated is acceptable, provided she is informed of the potential risks and benefits. This might include cases where women are of the opinion that benefits of symptom relief outweigh potential risks following unsuccessful attempts to stop HT, or women at high risk for osteoporotic fractures who experience moderate to severe menopausal symptoms.²¹ For this group of women it might be necessary to not adhere to the concept of the lowest dose for the shortest time, but to rather use the lowest dose for as long as is necessary.

The only individual in a position to answer the question if we should stop HT at age 65 years will be the woman for whom the use of HT might be indicated after the age of 65 years. What she needs is guidance and information as well as proper clinical supervision provided by her health care provider.

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