

## Use of Hormone Replacement Therapy in the Asymptomatic Postmenopausal Woman: What is the Current Evidence?

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### Abstract

*The publication of the Women's Health Initiative (WHI) Study results in July 2002 has changed the understanding of the use of hormone replacement therapy (HRT) in the postmenopausal woman, and challenged many of the accepted dogmas culled from decades of observational studies. The results of the WHI demonstrated a small but significant increased risk of coronary heart disease, strokes, pulmonary embolism and breast cancer amongst women who used continuous combined HRT. Conversely, there was a decreased risk of colonic cancer and osteoporotic fractures. However, the net balance of risk and benefit for long-term use of combined HRT has shifted towards the negative. In the light of the above findings, and together with the many associated studies that have since been published, the indications of HRT need to be reviewed. When the patient has disturbing vasomotor symptoms with compromised quality of life, HRT is clearly indicated for the relief of symptoms. As these symptoms are often transient, the period of therapy is usually short term. The situation is less clear among patients who do not have vasomotor symptoms, but nonetheless suffer from long-term degenerative changes of oestrogen deficiency. This article explores the implications for HRT in this post-WHI era, and seeks to define valid indications and conditions for its use.*

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*Key words: Hormone replacement therapy, Menopausal symptoms, Women's Health Initiative*

### Introduction

The understanding of hormone replacement therapy (HRT) for postmenopausal women has undergone dramatic change since the publication of the results of the Women's Health Initiative (WHI) study in July 2002.<sup>1</sup>

WHI is the first large prospective, double-blind, placebo-controlled, randomised controlled trial on the use of combined HRT among healthy postmenopausal women. It studied over 16,000 women over a mean period of 5.2 years. The results of the WHI showed a small but significant excess number of adverse coronary events among women who were assigned to use combined HRT when compared with women on placebo. This has severely challenged the widely accepted dogma over the past decades that HRT is able to significantly reduce the risk of coronary heart disease in postmenopausal women.<sup>2-4</sup> In addition, there were demonstrable increased incidence of strokes and pulmonary embolism among women using combined HRT. The debate over the risk of breast cancer<sup>5</sup> with long-term use of combined HRT has been largely settled with the

conclusion that for women using combined HRT, there was a small but noticeable increased risk after more than 4 years of treatment. Further, mammographic changes among women on combined HRT may have made it more difficult to detect cancerous change.<sup>6</sup> While the benefit of protection against osteoporotic fractures and a reduced risk of colon cancer has been amply demonstrated, the overall balance of risk and benefit has been shifted towards the negative, particularly with long-term use.

As a response to these findings, many professional and governmental agencies<sup>7-9</sup> have moved to issue health advisories on the indications of use of HRT. The thrust of these recommendations was to restrict the use of combined HRT for women with intact uteri primarily for treatment of menopausal symptoms, using the lowest possible effective dose, and over the shortest time period.

This article seeks to put in perspective the findings of the WHI and other related studies. In particular, it seeks to answer the title question on the role, if any, of HRT in asymptomatic postmenopausal women.

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### The WHI in Perspective

Prior to the WHI, many of the deeply held opinions about the effects of HRT were based primarily on observational studies. These studies, when well conducted, may give us a good idea on the effects of HRT in the postmenopausal women, but unfortunately lend themselves to the problem of selection bias. Some of the benefits seen with HRT in the older observational studies may be due to the phenomenon of the “healthy-user” effect, i.e., HRT users may be more health conscious, and therefore take greater care in observing healthy life-style habits, which in turn lead to better health outcomes. The study design of the WHI, in prospectively randomising subjects to HRT treatment or placebo in a double-blinded fashion, effectively removed those biases present in the older studies. Hence, the results of the WHI have been keenly awaited by both supporters and critics of HRT alike.

The WHI<sup>1</sup> demonstrated that when combined HRT, in the form of conjugated equine oestrogens 0.625 mg in combination with medroxyprogesterone acetate 2.5 mg, was used among a large group of generally healthy postmenopausal women with intact uteri between the ages of 50 and 79 years over an average period of 5.2 years, the overall balance of benefits and risks tipped towards the negative. For every 10,000 women using such a preparation over a 1-year period, there would be 7 excess coronary heart events, 8 additional cases of pulmonary embolism, 8 additional cases of strokes and 8 additional cases of breast cancer when compared with non-users. Conversely, there would be 5 fewer cases of osteoporotic fractures and 6 fewer cases of colon cancer. The net effect is that there will be an excess of 19 cases of negative events per 10,000 women-years.

Does this mean that HRT should never be used under any circumstances? This would appear to be the conclusion if one were to read only the headlines in the lay press.

It should be highlighted that the absolute increase in adverse events was small. For the individual woman, the increased risk of breast cancer amounted to less than 0.1% per year.

Some 15% of postmenopausal women will experience significantly disturbing menopausal vasomotor symptoms.<sup>10</sup> Oestrogens remain one of the most effective methods in dealing with these symptoms. The efficacy of HRT in relieving menopausal vasomotor symptoms has been amply demonstrated in several prospective randomised controlled trials.<sup>11-14</sup> A significant improvement in quality of life can be expected with the use of hormone replacement in such women with symptoms: oestrogen alone for women who has had a hysterectomy, and combined oestrogen-progestin replacement for women with intact uteri.

While there has been much interest in the role “natural

alternatives”, such as phytoestrogens, many of the prospective randomised trials have failed to demonstrate its efficacy.<sup>15,16</sup> Much of the “feel good” effect may be attributed to a placebo effect.<sup>17</sup>

The hot flush, which is by far the most disturbing among the host of menopausal symptoms, tends to be limited to the perimenopausal period and seldom persist beyond the first 5 years of the postmenopausal period.<sup>10</sup> Hence, the anticipated period of treatment is likely to be short. For the symptomatic postmenopausal woman, HRT remains one of the best therapeutic choices available when used under close medical supervision.

### Type of Oestrogen/Progestin, Dose, Route of Administration and the Age of Postmenopausal Women

The publication in July 2002 which examined the effects of combined HRT on women with intact uteri was only one arm of the WHI study. This arm of the study was terminated prematurely owing to the excess incidence of adverse events. The other arm of the study, which examines the effects of oestrogen alone (Premarin) in women who have had a hysterectomy, is still ongoing, leading to the inference that the risk/benefit ratio may be different, and perhaps even favourable. Any such conclusion would be premature and it would be best to reserve judgement until the analysis of data from the second part of the WHI study, which will be available in 2005.

However, legitimate questions do arise from the WHI results. Would the choice of a different oestrogen or progestin have made a difference? Or perhaps a parenteral route of administration (e.g., patches or implants) as opposed to oral tablets, which suffers from a first-pass effect on the liver? For the moment, until further information is available, one cannot assume that other types of oestrogen or progestin preparation would be any safer than that used in the WHI study.

Would a more appropriate dosing (e.g., lower doses for the older women) have allowed for a more positive result particularly among the older patients? One criticism against the WHI study has been that the study subjects were much older compared to the typical woman on HRT (who are largely in their 50s). The mean age of the study subjects in the WHI was 63 years, and more than 60% of the cohort were in their 60s and 70s. Indeed, is using full dose HRT in 70-year-old women a wise clinical decision?

Results from the earlier Heart and Estrogen/Progestin Replacement Study (HERS) study have suggested that older postmenopausal women may be better served with lower than conventional doses.<sup>11</sup> Indeed, there is much interest in exploring lower dose alternatives, and preliminary data on its efficacy and reduced side effects are promising.<sup>18</sup> It will be a long while yet before this hypothesis can be fully

verified in a trial of a scale comparable to the WHI.

### **Is There Evidence to Support its Use in Asymptomatic Women?**

What then is the role of HRT in the asymptomatic postmenopausal woman? What are the indications for its use, if any?

#### *Asymptomatic Women and Quality of life*

Menopausal symptoms may be nebulous. The most disturbing is perhaps vasomotor symptoms, which responds well to treatment with oestrogen replacement. But does this mean that a woman without vasomotor symptoms, but complaining only of skin or vaginal dryness has only trivial complaints? Or even that they are asymptomatic?

Some symptoms (such as vaginal dryness) are more specific to oestrogen withdrawal than others, and thus respond more consistently to oestrogen replacement. Many of the symptoms have multiple origins, and oestrogen replacement may not be the most efficacious way of dealing with them. For example, the most common complaint among menopausal women in Singapore is muscle and joint pains.<sup>10</sup> Oestrogen replacement has not been shown to have any therapeutic effect on such symptoms.

Arising from the WHI study, the effects of oestrogen plus progestin on quality health-related quality-of-life indicators were also studied.<sup>19</sup> Aside from improvement of vasomotor symptoms experienced by women age 50 to 54 years, there were no other benefits in terms of quality-of-life outcomes. Specifically, the women randomised to receive oestrogen plus progestin did not have any improvement in general health, vitality, mental health, depressive symptoms or sexual satisfaction. A very small benefit was seen in terms of sleep disturbance, physical functioning and bodily pain in the short term.

The above would suggest that the use of combined HRT in women without vasomotor symptoms, but hoping to generally improve their quality of life, cannot be truly justified on scientific grounds. However, it is important to note that the WHI was not designed to examine the effect of HRT on vasomotor and other menopausal symptoms. Only 12% of patients in that study reported moderate to severe vasomotor symptoms at baseline. Trials looking specifically at symptoms and quality of life have demonstrated benefit.<sup>20</sup>

It should be emphasised that in clinical practice, management of an individual patient is not quite the same as conducting a clinical trial. Notwithstanding the good intentions of practicing evidence-based medicine, patients often rely on their perceived response to therapy to make decisions on whether or not to continue their HRT. Placebo effect or not, many patients who feel well on HRT are

reluctant to discontinue their treatment. They often feel that their youthful appearance and enhanced vitality is due in no small part to the HRT that they are on. This is a quality which cannot be measured with any accuracy. Perhaps our science does not yet have the sensitivity to quantify such a parameter.

If no demonstrable increased adverse events were demonstrated with long-term use, there would not be any concern over the indefinite use of HRT for indications such as “maintaining the youthful appearance and vitality”. However, the small but demonstrable increase in adverse events as documented in the WHI study makes it important that patients who continue HRT for long term in the absence of vasomotor symptoms do so only on the clear understanding of the risks involved. In such situations, the lowest possible dose should be used. The litmus question that should be posed to them is: “Is your quality of life improved with HRT?” If the answer to the question is no, it is clear that HRT should be discontinued.

The role of the attending physician should be to advise on the individual indications of the patient, and assess this against her risk profile. The advice on HRT should be tailored to the need of the patient. Where local treatment is effective (e.g., estrogen cream or tablet for atrophic vaginitis), long-term systemic treatment may be avoided. In principle, the lowest dose effective option over the shortest time period should be considered.

#### *Other Indications of Use*

It is abundantly clear after studies such as the HERS<sup>21</sup> and WHI<sup>1</sup> that combined HRT should not be used for the reduction of risk of coronary heart disease, regardless of whether the patient is at low or high risk for the disease.

However, it has also been demonstrated that postmenopausal women on HRT will experience a decreased incidence of osteoporotic-related fractures and incidence of colon cancer.<sup>1</sup> Unfortunately, these treatments are long-term interventions, and the results have shown quite clearly that the balance of risk and benefit in such situations was in the negative.

If the prevention or treatment of osteoporosis is the only indication for use of hormone replacement, alternatives should be considered. With the many effective and powerful alternatives currently available, ranging from selective oestrogens receptor modulators (SERMs), such as raloxifene,<sup>22</sup> to bisphosphonates, such as alendronate,<sup>23</sup> combined HRT should not be the first agent of choice to either prevent or treat osteoporosis. However, when these alternatives are not available for a patient with osteoporosis, or if significant vasomotor symptoms are present concurrently, HRT is a reasonable option.

There were numerous studies attesting to the neurotrophic and neuroprotective effects of oestrogen<sup>24</sup> and hence much speculation that HRT use may be useful to delay the onset of Alzheimer's disease.<sup>25</sup> However, the follow-up study of the WHI<sup>26,27</sup> which demonstrated the lack of any such benefit on cognition and, in fact, increased the risk of dementia in older postmenopausal women above the age of 65 years, have all but demolished this hope. It has been speculated that this may be partly due to the small increased risk of thrombotic events or mini-strokes, a condition that has been shown to be increased among combined HRT users.<sup>28</sup>

### Premature Menopause and Early Surgical Menopause

Thus far, the discussion has generally centred on the use of HRT in postmenopausal women after 50 years of age. Women who suffered from premature menopause, either naturally or by surgical intervention, are a distinctly different group of patients and merit special consideration. The WHI results did not address such a group of women.

The patho-physiology of oestrogen deprivation in women in their 20s, 30s and early 40s may be quite different from women who menopause normally in their 50s.<sup>29-31</sup> Certainly, the needs, functions and priorities of woman in their 30s are very different from those in their 60s. Hence, providing HRT for a young woman who has lost her normal reproductive hormones up to the average age of menopause is probably more physiological than replacing reproductive hormones for a woman beyond the average age of natural menopause.

We do not as yet have prospective randomised data on the exact risk/benefit ratio of HRT for premature menopause, but the clinical indication to assist the many bodily functions that oestrogens normally facilitate in such young women is compelling.

### Conclusion

The results of the WHI have changed our understanding of the effects of combined HRT in postmenopausal women. The strongest indication for the use of HRT in postmenopausal women is for the treatment of vasomotor symptoms, and symptoms specific to oestrogen deficiency such as vaginal dryness. There is little evidence to support the use of HRT for other indications, although many women on long-term HRT continue to do so with the faith that it maintains their youthful appearance and vitality. Such patients should be made aware of the risk/benefit equation. An exception may be made for women who suffer from premature menopause (either naturally or surgically), where there are compelling benefits from the use of HRT. For women whose sole indication of use is the prevention or treatment of osteoporosis, effective alternatives that are currently available should be considered.

The science of HRT is constantly being challenged by new findings, and we need to renew our understanding in the light of new information. We eagerly await the results of the second arm of the WHI study to clarify the risk/benefit equation for hysterectomised patients who are on unopposed oestrogen therapy.

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## QUESTIONS

1. In the WHI study:
    - a) There was a significant increase in adverse coronary events in women on combined HRT compared with placebo.
    - b) There was an increased incidence of pulmonary embolism and strokes in women using combined HRT.
    - c) Women on combined HRT have reduced risk of fractures from osteoporosis.
    - d) The risk of colonic cancers is decreased in women on combined HRT.
    - e) The risk of breast cancers is significantly increased after the first year of combined HRT treatment.
  2. Among postmenopausal women:
    - a) Fifty per cent of Singaporean women will experience disturbing vasomotor symptoms.
    - b) Oestrogens are more efficacious than phyto-oestrogens in alleviating menopausal symptoms.
    - c) Combined oestrogen-progestin treatment is advocated for women who have had a hysterectomy.
    - d) Hot flushes seldom persist beyond the first 5 years of the postmenopausal period.
    - e) HRT can improve symptoms of muscle and joint pain.
  3. In the WHI study:
    - a) The mean age of the study subjects was 50 years.
    - b) More than 60% of the subjects were between 51 and 60 years of age.
    - c) The mean period of use of HRT was 5.2 years.
    - d) For every 10,000 women using combined HRT for 1 year, there were 8 additional cases of breast cancers compared with a similar group of women on placebo.
    - e) For every 10,000 women using combined HRT in 1 year, there were 80 additional cases of pulmonary embolism compared with a similar group of women on placebo.
  4. a) Results from HERS suggest that women with a high risk of coronary heart disease will benefit from combined HRT.
    - b) HRT is the first option in the treatment of osteoporosis.
    - c) Biphosphonates are effective in treating osteoporosis.
    - d) SERMS are effective in treating the vasomotor symptoms of menopause.
    - e) SERM can prevent and treat osteoporosis.
  5. In WHI and associated studies
    - a) HRT was shown to improve cognition.
    - b) The risk of dementia in older postmenopausal women was diminished.
    - c) The risk of thrombotic cerebrovascular events is reduced in HRT users.
    - d) Women who underwent surgical menopause prior to the natural age of menopause were not included in the study.
    - e) Diagnosis of breast cancer may be hindered by mammographic changes amongst women on combined HRT.
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