Introduction

In July 2002, alarming news appeared in the world’s press and in other media suggesting that users of hormone replacement therapy (HRT) may be at increased risk of breast cancer and possibly cardiovascular disease. Until that time, there had been confidence that HRT was not only effective in treating acute menopausal symptoms, but that it also protected against osteoporosis and cardiovascular disease. Headline news appeared after the release of the initial results of Women’s Health Initiative Trial, a study conducted in the United States involving 16,608 postmenopausal women. Both patients and doctors panicked at the sight of these headlines. Almost immediately, countless women stopped using HRT, and many medical practitioners who used the press as their source of information stopped prescribing HRT due to concerns about risks. This article will seek to clarify current information about the risks and benefits of HRT.

HRT and Breast Cancer

The concern about breast cancer risk in users of HRT remains real, but for the WHI trial, the figures were released as percentage of risk rather than absolute risk. This exaggerated the risk perception. As it turned out, in absolute numbers, the difference in risk between users and placebo was small (Tables 1,2). For example, in women aged 50-59 years using HRT containing oestrogen as well as progesterone (the most common age bracket for HRT users in this region), there would be an estimated 3 additional cases of breast cancer per 1,000 women exposed to treatment over 5 years. More interestingly, in a WHI paper published later on the use of oestrogen by itself, in women aged 50-59 years there would be an estimated 4 fewer cases of breast cancer per 1,000 women exposed to treatment over 5 years. This reduction rather than increase in the number of cases of breast cancer with oestrogen treatment could not be fully explained. Not surprisingly, this apparent good news received little or no press coverage.

By far the most important indication for the use of HRT is the treatment of vasomotor symptoms (something that was not addressed in the WHI study). For this indication, HRT usually needs to be taken for only 1-2 years before the symptoms tend to subside. With this duration of treatment, the risk of breast cancer is no longer an issue. Oestrogen/progesterone therapy prescribed for up to 5 years does not add significantly to lifetime risk of breast cancer. Beyond that time, the increase in risk is small, and is comparable to other risks such as being obese or drinking more than 2 standard drinks of alcohol per day. Oestrogen-only therapy for up to 7 years does not significantly increase breast cancer risk. The recommendations of the Asia Pacific Menopause Federation (APMF) and also the International Menopause Society (IMS) state this clearly. Young postmenopausal women starting on combined HRT for the first time should be advised that breast cancer risks do not appear to increase in the first 7 years of use. Hysterectomised women on unopposed oestrogen are not at increased risk of breast cancer and some may even have a small reduction in risk.

HRT and Cardiovascular Disease

In the initial report of the WHI trial, study results showed a non-significant increase in coronary heart disease deaths and non-fatal myocardial infarction in the treatment group. However, in this so-called healthy population of women, the mean age was 63 years, their
mean BMI was 28.5, almost 40% had a history of smoking, 36% a history of treatment for hypertension and 13% had been treated for hypercholesterolaemia. It was already understood well before the WHI study that HRT was not to be used for secondary prevention of cardiovascular disease. Women with established cardiovascular risk are unsuitable for treatment with HRT as they already have diseased arteries, and the use of HRT may cause plaque instability.

However, as common sense would suggest, current evidence supports the cardioprotective effects of HRT when treatment is initiated in younger postmenopausal women (Table 3). Reanalysis of the WHI data itself has shown that there is a likely beneficial effect on the cardiovascular system for women who begin treatment with HRT at or near the time of the menopause5,6.

According to APMF and IMS guidelines, young healthy postmenopausal women can be started on HRT when clinically warranted without fear of increased cardiovascular disease risk. However, oral HRT should not be prescribed to women with a previous episode of venous thromboembolism. Women seeking HRT who have potential or confirmed risk factors for venous thromboembolism and stroke need individualised counselling; in these situations, transdermal HRT might be preferable to oral formulations.

### Table 3. HRT and coronary heart disease risk according to reanalysis of WHI data

<table>
<thead>
<tr>
<th>Years since menopause</th>
<th>HR for CHD</th>
<th>Risk 16,000 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 years</td>
<td>0.76 (0.50-1.26)</td>
<td>-6</td>
</tr>
<tr>
<td>10-19 years</td>
<td>1.10 (0.84-1.45)</td>
<td>4</td>
</tr>
<tr>
<td>≥ 20 years</td>
<td>1.28 (1.03-1.58)</td>
<td>17</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59 years</td>
<td>0.93 (0.65-1.33)</td>
<td>-2</td>
</tr>
<tr>
<td>60-69 years</td>
<td>0.98 (0.70-1.31)</td>
<td>-1</td>
</tr>
<tr>
<td>70-79 years</td>
<td>1.29 (1.00-1.65)</td>
<td>19</td>
</tr>
</tbody>
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Adapted from Roussos et al JAMA 2007:11:1405-77 (6)

**HRT and Osteoporosis**

HRT is effective in preventing the bone loss associated with the menopause and decreases the incidence of all osteoporosis related fractures, including vertebral and hip fractures, even in patients at low risk for fractures7. HRT is indicated for the prevention of bone loss in women with premature menopause and secondary amenorrhoea. It is also indicated in postmenopausal women in the age group 50-60 years presenting with a risk for fracture. Potential adverse effects of HRT can be limited by using lower than standard doses or by avoiding oral administration, without compromising the beneficial effect of HRT on bone.

Once again, APMF and IMS guidelines support the use of HRT as the most cost effective and relatively safe choice for prevention of fractures in women under 60 years of age. In addition, although some degree of fracture protection may remain after stopping HRT, the patient at risk for fracture should then receive other suitable therapy.

The continuation of HRT after the age of 60 for the sole purpose of the prevention of fractures should take into account the possible side effects in the individual of the specific dose and method of administration of HRT, compared to other proven therapies. The initiation of HRT for the sole purpose of the prevention of fractures is not recommended after the age of 60 years.

**Aftermath of WHI**

In the years since 2002, a number of things have become obvious. Firstly, the number of users of HRT dropped dramatically soon after the WHI announcement, and although there has been a slow increase in users of HRT, in most countries this has never returned to pre 2002 levels8.

The WHI study was a prospective placebo controlled study of the effect of hormone replacement therapy with the primary outcome being the effect on cardiovascular events. The effect on breast cancer was not a primary outcome indicator, and there was no examination of the effect of HRT on hot flushes. The WHI trial was supposed to be a trial using primarily healthy postmenopausal women. Before 2002 (and since 2002 for that matter), as clinicians we have mainly been prescribing HRT to treat vasomotor symptoms in women at or soon after the menopause (i.e. usually around 50 years of age). Most of the women we see are healthy and are non-smokers.

So why are both women as well as the doctors who care for them afraid of using HRT? The answer is obvious. Both groups still remember the headlines from 2002, and no headlines supporting the safety and benefits of HRT have been published since (because good news doesn’t make headlines).

**How Should I Advise My Patients?**

The importance of individual risk benefit assessment cannot be over emphasised. For women with troublesome vasomotor symptoms, oestrogen is far superior to all other treatments in terms of efficacy. In Hong Kong, postmenopausal Chinese women more commonly have relatively mild symptoms which may need no treatment or else lower dose HRT which often needs to be taken for two years or less. For these women, the benefit clearly outweighs the risk.

If women present for consultation at the time of menopause, this is an ideal opportunity to also assess the need for other interventions which may include advice on diet and lifestyle and screening for other medical conditions which become more common in this age group. Recommendations for examination and investigation by the Asia Pacific Menopause Federation are as follows:

- **First Visit:** General examination, including weight & height, blood pressure measurement, breast and pelvic examination.
Investigations: Advised: Pap smear, complete blood count, fasting blood sugar, fasting lipid profile.

Other investigations to be ordered on a case to case basis include: Liver function tests, thyroid function tests, mammography, bone mineral density, ultrasonography.

Summary

For the majority of healthy symptomatic women who have recently reached menopause, the benefits of low dose hormone replacement therapy outweigh the risks. Refusal to prescribe HRT for these women is against available medical evidence.

References

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