

Current attitudes toward hormone replacement therapy (HRT) prescribed during menopause

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Introduction

The use of postmenopausal hormone replacement therapy poses one of the most difficult health-care dilemmas women are facing today. The life expectancy for the average woman in the western world today has reached 83 years; part of the population will live a third of their lives in an estrogen-deficient state. Unfortunately, only 20% of these women receive any form of treatment [1].

Hormone replacement therapy (HRT) offers well-established benefits, including alleviation of vasomotor symptoms [2], management of urogenital atrophy and libido decline, prevention of osteoporosis and fractures and provides a possible cardiovascular protective effect and risk reduction of colon cancer [3].

However, some physicians are still hesitant to prescribe HRT. One reason may be that according to studies the long-term use of HRT might raise the risk of breast cancer. The confusion about the cardiovascular protective effects was supported by the Heart and Estrogen Progestin Replacement Study (HERS) [4], and the question has been posed whether long-term HRT use maintains bone density, but will not in the future diminish bone fracture risk.

Cardiovascular dilemmas

Observation studies on ERT/HRT suggested that heart disease risk is reduced by 35% to 45% in HRT users [5, 6]. The Heart and Estrogen/Progestin Replacement Study [4], was the first randomized clinical trial to examine the effects of HRT on women with established cardiovascular disease (CVD). Surprisingly, 52% of women on HRT experienced coronary events in the first year of the trial, but after four years of therapy there were fewer CHD deaths in women assigned to HRT. The authors concluded that women with CVD should not initiate HRT with only the goal of preventing future cardiovascular events.

The American Heart Association recommendation is based on recent scientific studies about the role of HRT in reducing the risk of coronary heart disease in postmenopausal women: for postmenopausal women who have had a heart attack or stroke, the guideline recommendation is that HRT should not be initiated for secondary prevention. Recently, a large retrospective study that evaluated the effect of ERT/HRT use for 114,724 women with confirmed myocardial infarction (MI), showed that ERT/HRT use was associated with a 35% improvement in the survival rate from MI [7]. In an editorial of this paper, Mendelsohn and Karas [8] point out that what actually can be learned from the HERS trial is that women with known CVD who are 20 years postmenopause are not protected from cardiovascular events if they are newly initiated on HRT. They concluded that HRT should not be prescribed for cardiologic purposes but for other purposes including alleviation of vasomotor symptoms or prevention of osteoporosis, which is our standard practice. Does HRT prevent CVD events in healthy women? The Women's Health Initiative (WHI) trial, designed to compare placebo use to HRT use, provided definitive answers about the value of HRT for the primary prevention of heart disease. The results indicate that this regimen should not be initiated or continued for primary prevention of CHD [46].

Osteoporosis dilemmas

Osteoporosis is a disease characterized by low bone mass with a consequent increase in fracture risk; for example a 10% reduction in bone mass doubles the risk of fracture [9]. Early diagnosis and treatment is the key. Once a fracture occurs there is an increased likelihood of additional fractures [10, 11]. A recent study [12] examined fracture risk within one year of the first incidence of fracture, and revealed that the percentage of patients experiencing a fracture will rise in accordance with the number of patients having pre-existing fractures. Therefore, it is very important to diagnose osteoporosis. Once it is diagnosed, treatment should start. Treatment options include maintaining adequate vitamin D and calcium intake, exercising, stopping smoking and in addition, considering pharmacological options. HRT remains the most preferred pharmacological choice for the prevention of osteoporosis in postmenopausal women, but its use has been limited by its side-effects. Observational studies have shown that HRT use reduces the risk of vertebral fracture by 50% to 80% and the risk of hip fracture by 25% to 30% [13], but data from randomized trials are limited. Recently, a meta-analysis [14] of 22 randomized clinical trials has shown that HRT significantly reduces the overall risk of non-vertebral fractures for women under 60 years old. An editorial comment for this paper was that until the efficacy of HRT is clarified, other treatment options should be the first choice for older women with osteoporosis [15].

Cancer dilemmas

Despite its many benefits, there is strong and consistent evidence that unopposed estrogen therapy, at moderate and high doses, is associated with increased rates of endometrial hyperplasia, irregular bleeding and consequent non-adherence to therapy [16-17]. The addition of oral progestogens administered either cyclically or continuously is associated with reduced rates of hyperplasia and improved adherence to therapy.

Irregular bleeding is less likely under sequential than continuous therapy but it has been suggested that continuous therapy over long duration is more protective than sequential therapy in the prevention of endometrial hyperplasia. Hyperplasia is more likely when progestogen is given every three months in a sequential regimen compared to a monthly progestogen sequential regimen [17].

However there is great concern about the potential risk of breast cancer with long-term use of estrogen [18], and that the addition of progestins may increase that risk [19]. Recently, an additional small case-control study concluded that recent long-term use of HRT is associated with an increased risk of breast cancer [20]. A Medline search of the literature from 1975-2000 was done by Bush *et al.* [21]. The purpose of the search was to assess recent epidemiological evidence that supports an association between the use of ERT/HRT and the risk of breast cancer. The conclusions were that there is no evidence to support the hypotheses that ERT increases the risk of breast cancer and that HRT increases the risk more than ERT. Although there is a lack of consistency regarding the risk of breast cancer with HRT, there is consistency regarding HRT use and both mortality rates and survival from breast cancer. The most important conclusion of the review is that additional observational studies are unlikely to alter their conclusions.

Colorectal cancer

Epidemiological studies have suggested that estrogen use may reduce the risk of developing colon cancer in women. A recent meta-analysis demonstrated that women who use HRT are at decreased risk of developing colon cancer [22]. Protection against colon cancer was greatest in recent users of HRT.

Recent HRT use was associated with a 33% reduction in the risk of colon cancer (RR = 0.67; CI 0.59-0.77). HRT use, however, did not protect against rectal cancer. In addition, there was also a suggestion, based on limited data, that HRT use may protect against death from colon cancer (RR = 0.72; 95% CI 0.64-0.81).

A recent retrospective case-control study from the Massachusetts Cancer Registry demonstrated similar findings [23]. This study also demonstrated that recent HRT use (> 1 year) was associated with a decreased risk of colon cancer (RR = 0.6; 95% CI 0.4-1.0), and that it did not protect against rectal cancer. Long-term use of HRT (> 5 years) was similarly protective (RR = 0.5; 95% CI 0.3-1.0).

Venous thromboembolism

Observational studies indicate that the postmenopausal use of estrogen increases the risk of developing deep venous thromboembolisms by a factor of 2 to 3.5. The finding in HERS among women assigned to

receive estrogen-progestin therapy is consistent with this estimate [24]. Because idiopathic venous thromboembolism is uncommon in women over 50 years of age, the absolute risk associated with the use of postmenopausal estrogen is relatively small (increasing the expected incidence by 20 cases per 100,000 woman-years).

Gallbladder disease

Several large observational studies have found that the risk of gallstones or cholecystectomy is increased by a factor of 2 to 3 in postmenopausal women who are taking estrogen. In HERS, the risk of gallbladder disease was 38 percent higher among women who were randomly assigned to receive estrogen-progestin therapy than among those assigned to receive a placebo [25].

Weight and body fat distribution

There is no evidence of any effect of unopposed estrogen or combined estrogen on body weight, indicating that these regimens do not cause extra weight gain in addition to that normally gained at menopause [26].

Physicians' approach

Guidelines and analyses of the benefits and risks of hormone replacement therapy are available for clinicians who counsel women about the use of postmenopausal hormones [27-34].

The rate of HRT use in menopausal women varies from 10 to 20% in different countries. Some studies have reported higher rates in well-educated women and women with higher incomes [35]. In Israel, about 12% of the postmenopausal population currently use HRT and about 10% more did so in the past [36].

Women gynecologists are more likely to be well informed about HRT. Thus their attitudes towards its use by their patients and by themselves are very important. Studies done among female gynecologists revealed 50-80% use of HRT [37-40] among their patients.

Scandinavian gynecologists are generally well informed about HRT and liberally recommend HRT for women without contraindications [41].

Controlling for age and practice type, HRT prescribing frequency was lower among male than female providers (odds ratio [OR] 0.38, 95% confidence interval [CI] 0.21-0.65), higher among providers who agreed (vs disagreed or neutral) that a convincing scientific case has been made that HRT prevents heart disease (OR 2.66, 95% CI 1.53-4.61), and higher among those in the upper tertial vs (OR 2.50, 95% CI 1.29-4.85). The conclusion of the study was that female providers and providers with positive attitudes toward HRT are the most likely to prescribe HRT for postmenopausal women [42].

Most of the physicians interviewed in Morocco were positively inclined towards the notion of prevention and in favor of hormonal treatment, and approximately half reported that they have prescribed hormone therapy. Gynecologists and male physicians prescribe hormones more frequently, as do physicians who are at private facilities [43].

Despite controversy about HRT in the published literature, the Ontario physicians survey reported similar reasons and patterns of prescription, pretreatment investigations, and surveillance of postmenopausal women using HRT. These results suggest that Ontario physicians' knowledge about HRT is consistent with recommendations in the published literature [44].

In a recent study [45] most gynecologists recommended HRT during menopause. For women with an intact endometrium, the preferred regimen (75% of the gynecologists) was continuous combined HRT while cyclical combined therapy was chosen by 15% of the gynecologists. No significant differences were found between physicians regarding indications and contraindications to HRT.

Treatment duration is subject to wide variations, from no time limit to discontinuation after 5 to 10 years. Dietary supplements are also popular, as is alendronate, alone or in combination with HRT, for severe osteoporosis.

Conclusions

Before prescribing postmenopausal HRT, clinicians should evaluate and outline for the individual patient the presence of indications, particularly menopausal symptoms and possible contraindications, and

weigh the risks and benefits of HRT against alternatives and to individualize therapy. Therefore, physicians need to be familiar with the published data and the medical background of each patient. The goal of every treatment is to restore the menopausal patient to the lifestyle and quality of life she had before entering menopause. My suggestion is that until definitive guidelines become available, an individualized approach should be applied with careful consideration of both the benefits and risks of treatment. However, the woman herself should make the final decision after she is well informed with all available information.

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