CASE REVIEW

Hormone Replacement Therapy: Changing Guidelines, Changing Practice

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Abstract: In the past decade our knowledge about the benefits and risks of hormone replacement therapy (HRT) has evolved substantially. This paper reviews these changes and their impact on published clinical practice guidelines. In the early 1990s, HRT was strongly recommended to all postmenopausal women for short-term use in the treatment of menopausal symptoms, and for long-term use in the prevention and treatment of osteoporosis and the prevention of cardiovascular disease. The risk of breast cancer associated with HRT was considered small enough to be of little consequence in comparison to its purported benefits. Data from three large RCTs were published during the late 1990s and early 2000s – the PEPI trial, the HERS trial, and the WHI trial. In summary, these trials have shown increases in breast cancer (9 per 10,000 postmenopausal women per year) and cardiovascular events (7 coronary artery events and 8 strokes per 10,000 postmenopausal women per year) that may not be balanced by the decreases in menopausal symptoms and osteoporotic fractures (57 fewer total fractures per 10,000 postmenopausal women per year) in women taking HRT. These findings have led to changes in clinical practice guidelines for HRT use. Current guidelines recommend against the use of HRT solely for the primary or secondary prevention of cardiovascular disease, and caution against its use for the sole purpose of osteoporosis prevention or treatment. Short-term relief of menopausal symptoms remains a relatively acceptable indication for HRT, however any prescription of HRT should be accompanied by a detailed discussion of its potential risks and benefits.

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Case Study

Shelagh, a 68-year old woman with hypertension, has been taking hormone replacement therapy (HRT) for the past 15 years. She initially began HRT for relief of menopausal symptoms but has continued on the recommendation of her previous physician, who told her it would help prevent cardiovascular disease. Her most recent bone mineral density (BMD) measurement shows slight bone loss but no osteoporosis. She wonders whether she should stay on HRT indefinitely.

There are currently some 5 million Canadian women over the age of 50, the majority of whom are post menopausal.[1] There has been a rising trend in HRT use amongst postmenopausal women, from about 10% in the early 1990s to about 35% in recent years.[2,3,4] Thus, any changes in our understanding of and recommendations concerning HRT will impact a large number of women.

Since the introduction of HRT, research has led to several significant changes in the clinical use of unopposed estrogen (ERT) and combined estrogen-progestin (HRT) therapies. In the 1970s and 1980s, evidence of increased endometrial cancer in ERT users led to the addition of a progestin in non-hysterectomized women. In the early 1990s, research supported the use of HRT for the prevention of cardiovascular disease but by the late 1990s, evidence was emerging that challenged that view.[4,5] The results of recent large scale trials of HRT are now changing HRT-prescribing practice once again.

Physicians who were practicing in the late 1980s and early 1990s are able to place these most recent changes in context, explaining the changes in recommendations to their patients. For newer physicians and those just learning the trade, the most recent studies and guidelines are often presented as current state-of-the-art knowledge without any historical context. For these practitioners, it can be difficult to understand the rationale for some women's HRT use. This can make balanced discussion, patient education about current medical knowledge and recommendations, and decision-making more difficult.

To help address this gap, this paper will explore the changes in knowledge and clinical guidelines about HRT use by postmenopausal women that have occurred over the past decade, focusing on osteoporosis, breast cancer and cardiovascular disease.

HRT and Menopause

It is widely accepted that estrogen therapy reduces vasomotor disturbances (hot flashes), vaginal epithelial atrophy and dryness, and other unpleasant symptoms experienced by women during menopause.[4,5,6] In general, guidelines agree that if ERT/HRT is chosen for the relief of menopausal symptoms, it should be implemented with the lowest effective dose and for the shortest time period possible – usually about 5 years, given that hot flashes naturally tend to diminish within 3-5 years and rarely persist longer than 7 years.[7,8,9,10]

Canadian guidelines from the early 1990s state unequivocally that the benefits of HRT in terms of menopausal symptom relief clearly outweigh its risks.[4] More recent guidelines, which incorporate new evidence concerning the risks of HRT, recommend that clinicians discuss the risks and benefits of HRT with every woman prior to its prescription for the relief of menopausal symptoms.[9,10,11]

HRT and Osteoporosis

The effectiveness of ERT/HRT in preventing osteoporosis has been evaluated using bone mineral density (BMD) and

fracture incidence as the outcomes of interest. Although BMD is useful as an objective measure of therapeutic effect on bone mass, fracture incidence is the outcome of greatest clinical importance. To be of use, fracture incidence with therapy must be compared against baseline rates. Estimates of the baseline incidence of osteoporotic fracture in postmenopausal women range from 191 to 284 per 10,000 women (the mean value of 238 will be used for comparative purposes).[17,18,19]

Early data from observational studies of women taking ERT showed a 25-50% reduction in overall fracture rates, which would translate into 60-120 fewer fractures per year per 10,000 postmenopausal women. Some studies showed that the risk reduction increased with the duration of ERT use but once ERT was discontinued, bone mass was lost at a rate similar to that seen in untreated perimenopausal women and the risk of fracture increased. Within about 6 years, the risk of hip fracture was the same as it would have been if ERT therapy had never been administered.[6,12,13]

After the introduction of combined estrogen/progestin HRT, multiple studies demonstrated reduced loss of BMD with HRT. However, high-quality evidence concerning the effect of HRT on fracture incidence was lacking.[6,13,14]

On the basis of these data, early guidelines recommended consideration of ERT/HRT as preventative therapy for osteoporosis in all menopausal women but especially those at increased risk of osteoporosis due to family history, medical conditions, or other factors.[4, 8, 12] As stated by the American College of Obstetricians and Gynecologists (ACOG), "A generally accepted approach for the prevention of osteoporosis is a program of hormone replacement therapy, calcium supplementation, and exercise."[5] Others took a more conservative tone, recommending that decisions be made on an individual basis, considering personal risk factors and preferences.[13,15] It was recommended that such preventative treatment continue long term (6 to 20 years, or indefinitely) to avoid the rapid bone loss and increased fracture risk seen with discontinuation.[4,8,12,13,16]

The Heart and Estrogen/Progestin Replacement Study (HERS) was the first large scale randomized-controlled trial (RCT) of HRT to measure fracture incidence. In 2001 it reported that 4 years of HRT treatment failed to reduce fracture incidence in the subgroup of its participants who did not have osteoporosis, as assessed by BMD, at enrolment.[17] The open-label HERS follow-up study, published in 2002 with 6.8 years of data, found that fracture incidence was actually slightly higher in the group receiving HRT.[18]

The Women's Health Initiative (WHI) was the first RCT to provide evidence of a reduction in fracture incidence amongst women taking HRT.[19] Overall, it found a 24% reduction in hip, vertebral, and other osteoporotic fractures in women who had taken HRT for an average of 5.2 years. This would translate into a total of 57 fewer fractures per year per 10,000 postmenopausal women. Time trend analysis of the hip fracture data showed a cumulative benefit over time. It should be noted, however, that these values are based on data for all women enrolled in the study; no separate analysis has yet been presented for the subgroup of women who had no pre-existing osteoporosis at enrolment.

In 2002, on the basis of these data, the United States Preventive Services Task Force (USPSTF), the Society of Obstetricians and Gynaecologists of Canada (SOGC), and the Osteoporosis Society of Canada (OSC) all published revised guidelines concerning HRT and osteoporosis.[1, 20,21] To summarize these, HRT is recommended for the prevention of further bone loss in women with osteopenia. In all other postmenopausal women (those with normal bone mass and those with osteoporosis), decisions regarding the use of HRT for the primary prevention or treatment of osteoporosis should be made in light of patient risk factors and preferences. Clinicians are encouraged to consider other therapies and strategies for preventing osteoporosis and fractures.

HRT and Breast Cancer

Estimates of breast cancer risk with HRT must be compared against the baseline risk for the population. The incidence of breast cancer in postmenopausal women has been estimated to be 23-47 per 10,000 women per year (mean value of 35).[6,18,19,22,23]

In the 1970s and 1980s, a number of case control and cohort studies showed no consistent evidence of increased breast cancer risk when ERT was used for less than 5 years but did show a trend towards increased risk with longer-term use. A meta-analysis estimated a summary relative risk of 1.25 (95% CI, 1.04-1.51) for women who took ERT for more than 8 years.[6] If true, this translates into an additional 9 breast cancers per year per 10,000 women taking long-term ERT.

The data from the 1980s, after the introduction of HRT, was more limited and no pooled estimate of HRT-associated breast cancer risk was available in the early 1990s.[6] Guidelines issued at that time varied in their position on ERT/HRT and breast cancer. Some included statements such as, "Physicians ... can be reassured that, to date, estrogen replacement for less than 15 years' duration appears to have little, if any, effect on the risk of breast cancer." [4,5] Others took a more conservative tone, such as, "The risks of hormone therapy may outweigh its benefits in women who are at increased risk for breast cancer. For other women, the best course of action is not clear."[8]

By 1997, sufficient non-randomized prospective and case control studies of HRT use and breast cancer had been conducted to allow quantitative meta-analysis. Overall, the use of HRT was associated with an increased relative risk of breast cancer of 1.14 ($p<0.01$).[24] This finding would translate into an additional 5 breast cancers per 10,000 postmenopausal women per year. With 5 or more years of HRT use, the relative risk of breast cancer was 1.35 (95% CI 1.21-1.49), which translates into 12 additional cases of breast cancer per 10,000 women per year.[23]

Guidelines in the late 1990s consequently took a more uniformly conservative tone but continued to recommend

consideration of HRT for all postmenopausal women.[11,13,15]

In 2002, the HERS research group published its finding of a statistically non-significant 27% increase in breast cancer incidence in women who had taken HRT for a mean of 6.8 years, compared to women who had taken placebo. However, breast cancer was not a primary outcome in HERS and the study was not designed with sufficient power to detect small but potentially significant changes in breast cancer incidence.[17,18]

The WHI was the first RCT to show an increased risk of breast cancer with HRT use. In 2002, the HRT arm of the trial was halted prematurely due mainly to the finding of a 26% (hazard ratio (HR) 1.26, 95% CI 1.00-1.59) increase in invasive breast cancer, but no difference in *in situ* breast cancers, amongst women who took HRT for a mean of 5.2 years, compared to women who took placebo. This finding amounts to an increase of 9 invasive breast cancers per 10,000 women per year. Time trend analysis showed that breast cancer risk was similar for both treatment groups over the first 4 years but then diverged, with the breast cancer risk in the HRT group rising more quickly thereafter. Subgroup analysis showed an increased breast cancer risk in women who had taken HRT prior to enrolment in the study. The authors suggest this may be the result of a cumulative effect of estrogen/progestin exposure.[20]

On the basis of HERS, WHI, and earlier observational studies, several government and professional bodies have issued updated recommendations over the past year.

The USPSTF concluded that there is good evidence for an increased risk of breast cancer with HRT and currently recommends against the routine use of HRT for the primary prevention of chronic disease. As they stated, "the harmful effects of estrogen and progestin are likely to exceed the chronic disease prevention benefits in most women."[20]

In their 2003 statement on the WHI findings, the SOGC concludes that "[c]ombined continuous HRT should not be recommended routinely for all postmenopausal women because ... the slightly increased risk[s] of cardiovascular disease and breast cancer outweigh the benefits in asymptomatic women."[25]

This discussion has focused on breast cancer risk in the general population of postmenopausal women, but clinical decisions regarding HRT and breast cancer are often more complex than this summary indicates for women with a family or personal history of breast cancer.[19,26]

HRT and Cardiovascular Disease

Cardiovascular disease (CVD), including both coronary artery disease (CAD) and cerebrovascular disease, is the leading cause of death amongst women in North America.[13,30,34] The incidence of CVD in women rises steeply during the sixth decade of life, simultaneous with the onset of menopause. Thus the majority of women's deaths attributable to CVD occur in postmenopausal women.

Estimates of baseline incidence rates vary with the age of women involved and known CVD risk factors. Overall, there are up to 30 CAD events and 21 strokes per 10,000 postmenopausal women per year.[19,32] In postmenopausal women with a previous history of CAD or stroke, these rates rise sharply to 370 CAD events and 195 strokes per 10,000 women per year.[27] With these incidence rates, even small changes in the relative risk of CVD associated with ERT/HRT use could have a significant clinical impact.

Based on the observations that CVD risk rises steeply after menopause and that women who experience early surgical menopause are at higher risk for CVD than other women their age, it has long been postulated that estrogen is cardioprotective.[5] Early meta-analyses of ERT supported this proposition, finding a 35-50% decrease in the risk of CAD events and a 4% decrease in the risk of stroke.[6,25] Although these meta-analyses were based primarily on retrospective case-control and cohort studies, the uniformity of the positive findings led to little questioning of the overall conclusion and general acceptance that ERT reduced CVD risk.

The addition of a progestin has, since its introduction, been considered to attenuate ERT's CVD benefit. In the early 1990s little evidence concerning the effect of combined HRT on CVD risk was available and no pooled estimates of risk with HRT were calculated in early meta-analyses.[6,25]

The general acceptance of ERT as cardioprotective and the uncertainty concerning the effect of HRT were reflected in guidelines and consensus statements from the early 1990s.[5,8,29] Lobo *et al.* concluded that, "[b]ecause of the magnitude of CVD as a cause of morbidity and mortality, the beneficial role of estrogen in the primary prevention of CVD in most women outweighs its potential risks."[30] Indeed, if the pooled risk estimates from early epidemiological studies were considered true, they would predict a fall in the overall incidence of CAD events (from 30 to 15-19 new cases per 10,000 postmenopausal women per year).

The American College of Physicians (ACP) recommended that, "Women who have coronary heart disease or who are at increased risk for coronary heart disease are likely to benefit from hormone therapy." They qualify this with summary statements concerning the evidence: "There's extensive and consistent evidence that [unopposed estrogen] therapy reduces the risk for coronary heart disease. ... Combination therapy may also reduce the risk for coronary heart disease, but data are not sufficient at this time to estimate the magnitude of the risk reduction."[8]

The SOGC also recommended estrogen therapy for the prevention of CVD in postmenopausal women. However, in contrast to the other guidelines, this Canadian body also concluded that, "The addition of recommended low doses of progestin does not appear to alter the cardioprotective effect of estrogens."[4]

In the mid-1990s, two major studies published results suggesting that HRT with estrogen and progestin has a cardioprotective effect. In 1995, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial reported that a combined estrogen-progestin preparation elevated HDL-cholesterol and lowered LDL-cholesterol to a similar extent as an estrogen-only preparation.[30] In 1996, with 14 years of

follow-up data on women taking HRT, the Nurses' Health Study published their finding that the risk of major coronary disease was decreased by 61% (RR 0.39, 95% CI 0.19-0.78) in current users of HRT as compared to never users of ERT/HRT. They found no significant change in the relative risk of all stroke (RR 1.09, 95% CI 0.66-1.80), and a non-significant increase in the risk of ischemic stroke (RR 1.42, 95% CI 0.73-2.75) among current users of HRT.[31]

As a result, in May 1998, the SOGC published an update of its HRT recommendations, concluding that, "In the long-term, HRT appears to provide significant protection against cardiovascular disease... ." [11]

Soon thereafter, in August 1998, the HERS trial of HRT for the secondary prevention of CAD reported no significant difference in CAD deaths (RR 1.24, 95% CI 0.87-1.75) or nonfatal myocardial infarctions (RR 0.91, 95% CI 0.71-1.17) between women who took HRT for an average of 4.1 years compared to placebo. All women enrolled in this study had a known history of cardiovascular disease so these data may not reflect the true effect of primary preventative efforts, but they did throw into question the then well-accepted notion that HRT is cardioprotective. They also presented time trend analyses that showed declining harm over time and possible benefit after 4-5 years of treatment. They did not recommend starting HRT for secondary prevention of CAD but concluded that, "given the favourable pattern of [CAD] events after several years of therapy, it could be appropriate for women already receiving hormone treatment to continue."[32]

As a result of these findings, guidelines of the late 1990s focused on the balance between possible CVD benefits and emerging evidence of breast cancer risk. The ACPM concluded that, "There is insufficient evidence to make a generalized recommendation for or against HRT use by all menopausal women. ... Women with coronary risk factors... may benefit from HRT even if they have a family history of breast cancer... Current evidence favors indefinite use of HRT once initiated."[13] The American Heart Association (AHA) recommended against the use of HRT for secondary prevention of CVD and found that there was "insufficient data to suggest that HRT should be initiated for the sole purpose of primary prevention of cardiovascular disease."[33]

Most recently and definitively, the WHI published its findings of increased CAD and stroke risks with HRT after 5.2 years of follow-up. CAD events were increased by 29% (HR 1.29, 95% CI 1.02-1.63) and stroke by 41% (HR 1.41, 95% CI 1.07-1.85).[19] Annual rates of CAD events were increased from 30 to 37 events per 10,000 postmenopausal women. Stroke incidence was increased from 21 to 29 events per 10,000 postmenopausal women. Time trend analyses indicated that the increased risk for CVD began shortly after randomization and continued throughout the duration of the study. These increased risks were seen in women with and without a documented history of CVD. The authors concluded that their findings supported the AHA recommendation against HRT for secondary prevention and added their recommendation that HRT "should not be initiated or continued for the primary prevention of cardiovascular disease."[19]

This evidence was translated into altered guideline recommendations within a year of its publication. The USPSTF concluded that, "HRT does not decrease, and may in fact increase, the incidence of [CAD]." They went on to recommend against the routine use of HRT for primary prevention of chronic conditions, including CVD, in postmenopausal women.[20]

Similarly, the SOGC recommended that, "[HRT] should not be initiated or continued for the sole purpose of preventing future cardiovascular events (primary or secondary prevention)."[1]

Summary

The evidence concerning benefits and risks of HRT use has evolved substantially over the past decade. In the early 1990s, HRT was strongly recommended to all postmenopausal women for short term use in the treatment of menopausal symptoms, and for long-term use in the prevention of osteoporosis and cardiovascular disease. The risk of breast cancer was considered small enough to be of little consequence in comparison to the purported benefits.

Data from three large RCTs were published during the late 1990s and early 2000s – the PEPI trial, the HERS trial, and the WHI trial. As detailed above, the findings of these trials challenged many widely held beliefs about HRT and have led to a progression of changes in the clinical practice guidelines for HRT use. Current guidelines recommend against the use of HRT solely for the primary or secondary prevention of cardiovascular disease, and caution against its use for the sole purpose of osteoporosis prevention. Short-term relief of menopausal symptoms remains a relatively acceptable indication for HRT. However, any decision about HRT should be accompanied by a discussion about its risk-benefit ratio, seeking a balanced decision based on the available evidence, the woman's risk factors for cardiovascular disease, breast cancer, and osteoporosis, and the woman's preferences.

Ten years ago, when it was thought that HRT was cardioprotective, Shelagh would likely have been advised to stay on HRT to prevent the development of osteoporosis. Today, given her hypertension and the availability of alternative preventative therapies for osteoporosis, she should probably taper off her HRT. However, she should be encouraged to make her own decision following a detailed discussion about the known risks of CVD and breast cancer associated with long-term HRT, the probability that she would lose further bone mass if she discontinued HRT, and the availability of alternative therapies for prevention of osteoporosis. She would need to balance this information with her own perceptions of the risks and benefits.

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