

Current Status of Hormone Replacement Therapy in Post Menopausal Women

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Abstract: Assessment of the risks versus the benefits of hormone replacement therapy has become a challenging task for the physicians. Controversial issues have surrounded the status of hormone replacement therapy for postmenopausal women lately. Several randomized controlled trials present contradicting evidences and have raised questions about the short-term risks of long-term benefits of HRT. Evidence from clinical trials like the WHI and HERS trial does not support HRT use for prevention of cardiovascular disease. The review also discusses the association of hormone replacement therapy and cancer, stroke, cognition, cardiovascular disease, venous thromboembolism, osteoporosis, gall bladder disease, and quality of life. The latest controversial results of randomized controlled trials in recent years have posed newer challenges for the physicians in prescribing HRT for postmenopausal women.

INTRODUCTION

In 1999, approximately 38% of menopausal women in the United States underwent hormone replacement therapy [1]. The status of hormone replacement therapy for post menopausal women has been surrounded by controversial issues in the past year. Assessment of the risks versus the benefits of hormone replacement therapy has become a challenging task for the physicians. Since the past, many observational studies have supported the beneficial aspects of HRT. However, many recent evidence-based studies have highlighted that HRT use led to a decreased risk of atherosclerosis, osteoporosis fractures, along with no significantly increased risk of breast cancer [2]. In a study by Burkman *et al.*, low risks of colon cancer and Alzheimer's disease with HRT use were reported [3]. Another analysis in 1994 revealed benefits exceeding the risks with estrogen replacement therapy [4]. Improved longevity and decreased morbidity in 99% of US post menopausal women morbidity were proposed by another decision analysis [5].

Benefit in symptoms of menopause, improvement in quality of life, protection from cardiovascular disease and osteoporosis were some of the proposed benefits of HRT. However, in the past several years, evidence based medicine has brought forward the results of several randomized double blind placebo controlled trials, especially the results of Women's Health Initiative (WHI) study [6], which have radically affected routine prescribing of HRT in clinics. The randomized controlled trials present contradicting evidences and have raised questions about the short-term risks of long-term benefits of HRT.

HRT AND CARDIOVASCULAR DISEASE

The hormone therapy hypothesis suggests that hormone replacement after menopause is a method of mimicking the premenopausal state essentially, which should subsequently reduce CHD and osteoporosis in women. It has been demon-

strated that there has been an increase in the risk of coronary heart disease (CHD), stroke, venous thromboembolism and osteoporotic fractures after menopause in developed countries, accounting for a quarter millions deaths each year [7]. The Nurses Health Study reported that in women, who have undergone bilateral oophorectomy, the risk of coronary artery disease doubled as compared to those, who did not undergo surgical menopause [8].

Due to the action of estrogen on vascular function *via* genomic and nongenomic mechanisms, estrogen administration was thought to possibly confer cardioprotective benefits. [9]. The Heart And Estrogen/ Progesterin Replacement Study (HERS) was the first large randomized placebo controlled trial of estrogen for secondary prevention of CAD in postmenopausal women. Contradicting earlier observational evidence, the study showed little benefit of HRT as compared to placebo in patients of established coronary artery disease [10]. Rather, an increased risk of coronary heart disease events in the first year was observed, which was followed in subsequent years by a decreased risk. Initially, it was speculated that probably the duration of HERS was too short, but the recent results of HERS II with 6.8 years as follow up period reaffirmed the findings of the first trial [11]. HERS indicates that HRT does not decrease the risk of cardiovascular disease in women with established coronary artery disease.

In the estrogen replacement and atherosclerosis trial, 309 postmenopausal women with angiographically established coronary disease were randomized to receive estrogen (0.625 mg/day of conjugated equine estrogen) or estrogen plus progestin as HRT or placebo. A 3.2 yrs follow up revealed no effect on progression of coronary artery disease in any of the groups [12]. In the Postmenopausal Hormone Replacement Against Atherosclerosis Trial, 321 postmenopausal women were randomized to receive placebo or 1 mg/day of estradiol with gestodene (0.025 mg) administration from day 17 to day 28 every 4 or every 12 weeks. After 48 weeks no difference in atherosclerosis progression was noted in the treatment groups [13]. The Estrogen Prevention Of Atherosclerosis Trial also provided similar evidence. In the trial, 222 post

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menopausal women without preexisting cardiovascular disease and LDL cholesterol \geq 130 mg/dl were randomized to receive placebo or estradiol, with a reduced progression of atherosclerosis in the ERT group [14].

WOMEN'S HEALTH INITIATIVE TRIAL [6]

The WHI study was the first randomized primary prevention trial of postmenopausal HRT, sponsored by the National Institute of health and launched in 1991. A single dose of 0.65 mg CEE plus 2.5 mg medroxyprogesterone was used. The combined estrogen- progestin arm of WHI was stopped in 2002 due to a small increased risk of developing breast. An increase risk of ischaemic stroke and pulmonary embolism was also found. Beneficial effects included a decreased incidence of hip fracture and colorectal cancer. A subgroup of WHI on combination HRT enrolled in the Women's Health Initiative Memory Study (WHIMS), to assess the prevention of dementia with combination or estrogen only HRT. The trial was discontinued due to an increased risk of cognitive decline in the patients [15].

However, several flaws in the reporting of results of WHI have been pointed out by investigators [16]. The estrogen only arm of WHI was prematurely terminated in February, 2004 which concluded that there was no observed effect of estrogen alone in the incidence of coronary heart disease [17]. The scientists involved in WHI concluded that the risks increased in combination HRT outweigh the benefits and that it should never be used for cardiovascular protection, preservation of cognition or to prevent osteoporosis in a woman without any vasomotor symptoms. FDA has asked all manufacturers to list the findings of WHI and WHIMS clinical trials in term of black box warnings on the label of the product. Thus, evidence from clinical trials does not support HRT use for prevention of cardiovascular disease.

HRT AND VENOUS THROMBOEMBOLISM

An increase in the risk of venous thromboembolism was reported in both WHI and HERS, with the highest risk in the first year of use [19]. A meta-analysis conducted recently has revealed higher rates of venous thromboembolism, the highest risk with both estrogen and progestin being in the first year after initiation [20]. It has been postulated that short term HRT combinations increase thrombin and fibrin generation along with a reduction in plasma fibrinolytic inhibitory activity and increased fibrinolysis [21]. Differing effects of oral and transdermal oestrogen regimens on thrombotic parameters have been reported.

A role of factor V Leiden mutation and 20210, a prothrombin gene mutation have been implicated in increase risk of thrombosis with estrogen use. Women receiving HRT, particularly those having risk factors for thromboembolism are at increased risk of venous thrombolism. It is also advisable to screen for congenital thrombophilic disorders before prescribing HRT.

HRT AND STROKE

Contradictory results have been reported in various studies for effects of HRT on incidence of stroke. WHI study exhibited an increased risk where as some other studies reported a protective effect. The Women's Estrogen For Stroke

Trial, a randomized controlled trial for secondary prevention of cerebrovascular diseases failed to show a reduced incidence or mortality from stroke, thereby suggesting that the therapy was not indicated for secondary prevention with cerebrovascular diseases. The postulated mechanism for stroke exacerbation is not clear. The prothrombotic effects of HRT may account for increased risk of thrombosis. An increase risk of ischaemic stroke as compared to CHD risk has been reported possibly due to paradoxical embolism of leg vein thrombi in HRT users.

C reactive protein levels have also been found to be increased in some HRT users, however the WHI and some other studies did not exhibit any association or its modulation of CHD risk [22].

American heart association has formulated 'Evidence Guidelines For Cardiovascular Disease Prevention In Women' in 2004 about lifestyle interventions like cigarette smoking, heart healthy diet, along with major risk factor interventions like control of hypertension, dyslipidemia diabetes and preventive drug interventions [23]. The final results of the combination arm of Women's Health Initiative Trial reported a significantly increased risk at 5 years, primarily of non haemorrhagic stroke [24].

HRT AND CANCER

Breast Cancer

Estrogen is implicated in tumorigenesis in experimental animals [25]. The primary postmenopausal source of oestrogen production are the fat tissues in the body, including fat tissues in breast. Meta- analysis of available data has shown an increased risk of breast carcinoma. The Collaborative Group On Hormonal Factors In Breast Cancer showed no significant increase in breast cancer risk in 52000 women using HRT for less than 5 years, however, in women in estrogen replacement therapy, for greater than 5 years, a relative risk of 1.35 was shown [26].

Combined estrogen-progestin use has been associated with rather increased risk of breast cancer than estrogen used above in various trials [27].

However, evidence based, combined HRT arm of WHI study, which was terminated prematurely, showed that after 5.2 years, the risk of breast cancer was found to be increased by 26% in women taking combined HRT as compared to placebo group [6].

Women having one first degree relative with breast cancer are said to have an increased risk. Also women with BRCA1, and BCRA2 mutations have 70-80% increased lifetime risk of cancer. An alternative HRT regimen was studied in a cohort 3175 postmenopausal women most of whom received transdermal estradiol gel and a progestin (other than MPA). These women were followed up for 8.9 years and increase in breast cancer risk was found [28]. Similar contradictory results have been shown in the Nurses Health Study and in some other studies showing a reduction in mortality from breast cancer.

The use of HRT in women at risk of breast cancer is controversial, most of the recent randomized controlled trials showing an increased risk. Irrespective of family history and

other risk factors the results of WHI indicated an increased risk in women. Lifestyle modification and alternative therapies need to be explored further.

Endometrial Cancer

Higher dosage and prolonged duration of unopposed estrogen use has been associated with endometrial hyperplasia increasing the risk of endometrial cancer [29]. A meta-analysis of 29 observational studies has reported an increased risk of cancer in women prescribed unopposed estrogen as compared to non users. An increase in duration of use conferred higher risks. Another meta analysis reported a RR of 0.8 by combined regimens on endometrial cancer. However, neither HERS nor WHI studies reported an increased risk of endometrial cancer by combined HRT. So, the results of the evidence based studies differ from those of observational studies. Combined therapy is said to have not much role in prevention of endometrial hyperplasia.

Ovarian and Colorectal Cancers

There have been inconsistent results with HRT use as regards ovarian and colorectal cancer. The exact mechanism of ovarian cancer is not very clear. A direct carcinogenic action of ERT on ovarian cells to induce proliferation of ovarian cells has been confirmed by beneficial effects of tamoxifen in patient of ovarian cancer [30]. Also, hypothesized is a decrease in gonadotrophins by increased levels of estriol/estrone levels.

A large prospective study by American Cancer Society has proposed an increased risk of ovarian cancer and the associated morbidity and mortality in women who used estrogen for ≥ 10 years [31]. In a follow up of a nationwide breast cancer screening project by Lacey *et al.*, an increased risk was suggested in women using estrogen only as replacement therapy for ≥ 10 years [32].

Amongst evidence based studies, HERS study had shown no decrease in colorectal cancer risk in women which was contradicted by the results of WHI suggesting a decrease risk of colorectal cancer by estrogen. A meta-analysis of 18 studies corroborated with similar decrease in color cancer among HRT users as compared to non users [33].

HRT & Cognition

Observational studies have yielded mixed results. The Cache Country Study, a longitudinal observational study as regards prevalence and incidence of Alzheimer's disease, reported a decreased risk of Alzheimer's disease with HRT use for more than 10 years [34]. Two large meta-analysis published recently have combined the data from the 35 years regarding the effects of HRT on cognition and report a decreased risk of developing dementia in HRT users [35]. However, the evidence based studies differed again, when the WHI Trial authors reported that estrogen and progestin therapy increased the risk of probable dementia in women aged ≥ 65 years, updating it in 2004, that estrogen alone in led to an increase in risk for dementia and mild cognitive impairment [36].

Thus, recent trials have contradicted the earlier hypothesis that estrogen has a protection role against cognitive deterioration. The Alzheimer's Disease Cooperative Study use

oral CEE or placebo in women with a history of hysterectomy and established mild to moderate cognitive deficits. Most of trials published on HRT and cognition have methodological flaws and have yielded mixed results. Another double blind randomized placebo controlled trial in women, 75 years or over, with mild to moderate Alzheimer's disease failed to show any benefit by estrogen use [37].

HRT has been shown to improve depressive symptoms in perimenopausal women with no effect on symptoms of decreased libido, mood lability and loss of memory after menopause. The evidence supporting the role of HRT in preservation of cognition in healthy women or for treatment of Alzheimer's disease is weak as of now henceforth.

HRT and Osteoporosis

Evidence has accumulated that HRT leads to an increase in bone mineral density. HERS and HERSI had shown no benefit of HRT on prevention of osteoporosis. However, the recently published results of WHI report a decrease in hip fracture risk in HRT users [6]. In another meta-analysis, a 27% decrease in the incidence of nonvertebral fractures has been reported in women under 60 years showing greater risk reductions [38]. Another drug showing promise is bisphosphonates, which have shown benefit in BMD and estrogen preservation and thus a decrease in the hip fracture risk in 40-50% of women with osteoporosis. A decrease in spinal fractures had also been displayed by raloxifene, a selective estrogen receptor modulator [39, 40]. Thus, data supporting the use of HRT for a reduction in vertebral and nonvertebral fractures is limited and FDA has approved HRT use only for prevention and not for treatment of osteoporosis.

HRT and Gall Bladder Disease

The Nurses Health Study reported a positive association of HRT and cholecystitis in short term users of HRT with a relative risk (RR) of 1.8 [41]. HERS study demonstrated an increased rate of biliary tract surgeries in HRT users. WHI results have reported no such association however.

HRT and Quality of Life

Menopause brings with it distressing vasomotor symptoms like not flashes, nocturnal sweats, vaginal dryness, mood swings, and dyspareunia. HRT has been shown to improve these vasomotor symptoms bringing about relief in postmenopausal women. For long-term use, low dose regimens may prove to be more safe for use. Combined CEE and MPA therapy of at half the doses used in WHI has been equally efficacious in amelioration of vasomotor symptoms for young symptomatic women [42]. However, there is little evidence to support the contention, in elderly women [6]. Hlatky *et al.* had shown no benefit of hormone therapy on quality of life parameters, challenging the beliefs of remaining youthful and active by HRT use [43]. Furthermore a 2003 WHI report concluded that combined HRT therapy had no clinically meaningful effect on health related quality of life [44].

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

There is an impending need for future evidence based studies and trials with clear-cut primary outcomes. There is

an impending need for guidelines and analyses of benefits and risks of hormone replacement therapy. Recently the American Heart Association has published 'Evidence Based Guidelines For Cardiovascular. Prevention In Women' For Prevention Of CVD in women at increased risk. According to these guidelines, due to an improvement in CVD identification technologies, the distinction between primary and secondary prevention is not distinctly mentioned.

Lifestyle approaches for cardiovascular events prevention are recommended for all women. For women with established CAD, adjunctive therapy with ACE inhibitors, beta blockers, antiplatelet therapy is advised. It is now not justifiable to use HRT for cardiac disease prevention, rather the decision to choose HRT should be made by weighing non-coronary benefits and harms as advised by the American Heart Association.

For vasomotor symptoms in spite of being efficacious, HRT should not be considered as first line therapy. The WHI study has brought forward dramatic results about the health risks and benefits of HRT. Women >65 years or younger women at risk for osteoporosis should be advised routine BMD measurements along with calcium and vitamin D supplementation, weight bearing exercises and smoking cessation for fracture prevention. Clinicians should advise women of the absolute risks of HRT and avoid prescribing for CHD or stroke prevention or to women with clinical arterial disease. For prevention of osteoporosis, therapies like bisphosphonates or SERMS should be offered. The latest controversial results of randomized controlled trials in recent years have posed newer challenges for the physicians in prescribing HRT for postmenopausal women.

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