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Review Article

Hormone Replacement Therapy in menopause: current concerns and considerations

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Abstract
It has been estimated that one third of postmenopausal women in the U.S. use Hormone Replacement Therapy (HRT) to treat symptoms of menopause and prevent chronic conditions. In developing countries HRT use is not so common but there is an increasing trend in its use. It has been seen that women with better socio-economic status, higher education and urban population use HRT. It is important that benefits and harms of HRT based on scientific evidence should be considered when prescribing HRT. The health care workers should prepare themselves for a better dialogue with women including information about alternative treatment.
Objective: To review the available evidence on benefits and harms of HRT.
Methodology: A Medline search was done for papers published in English language between 1990 to 2003, with abstracts available. The limitations set were original articles and reviews. The key words used were Menopause, Hormone Replacement, HRT, and ERT. The local libraries were searched and email requests were sent for full text articles. 10 full text articles were available, mostly review and large studies, which were studied in more detail. Some textbooks and reference books for gynaecology were also reviewed.
Results: Beneficial effects of HRT on vasomotor symptoms have been supported by various studies, but HRT to treat negative mood is not recommended. A systematic review of Cochran database showed little evidence regarding the effect of hormone replacement therapy or oestrogen replacement therapy on overall cognitive function in healthy postmenopausal women. Oestrogens and androgens have significant beneficial effects on skin collagen, but do not prevent the effect of aging on elastic tissue and have limited use in the prevention and treatment of skin changes of menopause. Short-term benefits have been shown for urogenital atrophy. Recent evidences suggest that benefits of HRT include prevention of osteoporotic fractures, and colorectal cancer while prevention of dementia is uncertain. Harms include Coronary Heart Disease (CHD), stroke, thromboembolic events, breast cancer, with 5 or more years of use, and cholecystitis. It is recommended that the regimen should not be initiated or continued for primary prevention of coronary heart disease. In women with CHD, it should not be used for secondary prevention of CHD events. Active living, alternative therapies and consumption of food rich in phyto-oestrogens are some areas, which need to be explored in more detail. Conclusion: Patient preferences as well as evidence are important to initiate and/or continue HRT. Benefits and harms need to be re-addressed periodically to apply newly published evidence and to reassess emerging risk, co-morbidities and need of individuals.

An estimated one third of postmenopausal women in the U.S. use HRT[1] to treat symptoms of menopause and prevent chronic conditions. It has been seen that HRT users more often had better physical activity and better general health than non-users. Women with better socio-economic status, higher education and urban population were more likely to use HRT. Caution has to be exercised in assessing the benefits. More healthy profiles among HRT users may inflate the apparent benefit of treatment. It is a matter of concern that it also indicates existing inequalities in health and reduce any potential.[2, 3]

Benefits of HRT

A qualitative study[4] has shown that at collective level women acknowledge an increased risk of osteoporosis, and to a lesser degree of heart disease associated with menopause. At individual level, based mainly on their perceived risk on their family history and life style, women do not generally consider themselves to be at personal risk of disease. The study concludes that whilst women tend to associate menopause with an increased risk of disease, they do not generally consider themselves to be at personal risk, and in turn, choose not to take HRT for primary prevention.

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Another qualitative study[5] in African American women aged 30-65 years, majority of whom were past or current users of HRT, has shown that the women were aware of the medical indication for HRT and its risks and benefits. However, they expressed reservations about the use of HRT, and wanted a better dialogue with health care providers, including information about alternative treatment.

A study conducted in Sweden[6] has shown that women would like to pay even more than the cost of HRT to get rid of mild and severe symptoms of menopause like the vasomotor symptoms.

Benefits and harms of HRT based on scientific evidence should be considered when prescribing HRT given the background of cost, symptom relief, willingness to pay and risk of chronic condition for individual woman.

I. Vasomotor symptoms, psychological symptoms and mood changes

Vasomotor symptoms are found to be strongly related to the menopause, and these effects were not confounded or modified by previous psychological morbidity, social or behavioural factors.[7]

Beneficial effects of HRT on vasomotor symptoms have been supported by various studies, but HRT to treat negative mood is not recommended. [8]

II. Cognition and Dementia

A systematic review of Cochran data base in 2002 showed little evidence regarding the effect of hormone replacement therapy or oestrogen replacement therapy on over all cognitive function in healthy post menopausal women.[9] One study showed some effect on immediate recall and abstract reasoning, speed and accuracy in relatively young, surgically menopausal women. This study did not cover older women or those with menopausal symptoms. So the effect on cognitive function in these groups of women could not be determined. Another scientific review[10] has found some improvement in cognition, but they believe it could be due to improved sleep. Another study[11] has shown that addition of progestogens improved memory above what was obtained by oestrogen alone. They conclude that the effect did not depend on improvement of mood since the latter worsened during the progestogenic phase of HRT.

III. Genital tract, lower urinary tract and skin

Oestrogens and androgens have significant beneficial effects on skin collagen, but do not prevent the effect of aging on elastic tissue and have limited use in the prevention and treatment of skin changes of menopause.[12]

Short-term benefits have been shown by Hear and Estrogen Replacement study (HERS)[13] for urogenital atrophy. One study[14] has shown worsening of urinary incontinence throughout a 4-year period of HRT use.

IV. Coronary Heart Disease

Oestrogen in premenopausal women has a protective effect on cardiovascular disease probably mediated through its effect on High Density Lipoprotein (HDL): Low Density Lipoprotein (LDL) ratio, but oestrogen may work in other way such as by direct effect on blood vessels or by stimulatory vasodilatation via release of vaso active peptides and increased blood flow.[15]

Oestrogen therapy causes an increase in HDL and lowering LDL and total cholesterol concentrations, and the effects are greater with oral therapy following the first pass liver impact. Unlike synthetic oestrogen, natural oestrogens such as oestradiol and oestrone do not suffer from the disadvantage of increasing clotting factors, rennin substrate and insulin intolerance. Progestogens tend to raise LDL and lower HDL. It is however believed that the effects of oestrogen replacement therapy on serum triglycerides depend on the route of administration. Oral oestrogens, particularly conjugated equine oestrogens, induce hepatic synthesis of a specific protein component triglyceride rich lipoprotein, apo-lipoprotein B100 resulting in a rise in fasting serum triglyceride levels. Transdermal oestradiol leads to a statistically significant fall in serum triglyceride levels.[16]

But medroxy progesterone has less of this effect as compared to norgestrel and norethisteron. It is said that progestins also tend to oppose the beneficial effects of oestrogen on arterial dilation and blood flow. However earlier studies, including a 16 year follow up on nurses health study involving 121700 women of 59,337 women between 30-55 yrs. between 1976-1992, showed a marked decrease in the risk of major coronary heart disease among women who took oestrogen with progestin, as compared with the risk among women who did not use hormones. The study did not show significant association between stroke and use of combined hormones.[17]

The women's health initiative trail was conducted involving 16608 healthy post menopausal women aged 50-79 years with intact uterus through 40 US clinical centres in 1993-1998. Premarin 0.625 mg per

day and Medroxy Progesterone acetate 2.5 mg/day, and placebo was given to 2 groups of women. The mean follow up was 5.2 years. The estimated hazard ratio was CHD 1.29, Breast Cancer 1.26, Stroke 1.41, Pulmonary embolism 2.13, colorectal cancer 0.63, endometrial cancer 0.83, and hip fracture 0.66. The study concludes that the overall health risks exceed benefits from use of combined oestrogen and progestogen for an average of 5.2 years follow up among healthy postmenopausal US women. It is recommended that the regimen should not be initiated or continued for primary prevention of coronary heart disease.[18]

A randomized blinded placebo controlled trial of 4.1 years duration called heart & oestrogen progestin replacement study (HERS), and its subsequent unblinded follow up for 2.7 years duration (HERS II) was conducted at outpatient and community set up of 20 US clinical centres involving 2763 post menopausal women with coronary heart disease aged on an average 67 years at enrolment in HERS. 2321 women (93% of those surviving) were followed in HERS II. Oestrogen 0.625 mg and medroxy progesterone acetate 2.5 mg was given to the treatment group. No significant decrease in rates of primary CHD events (nonfatal MI or CHD death) or secondary cardiovascular events coronary re-vascularization, unstable angina, congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischaemic attacks and peripheral arterial disease was noted.

Lower rates of CHD events among women in the hormone group in the final years of HERS did not persist during additional years of follow up. After 6.8 years hormone replacement therapy did not decrease risk of cardiovascular events in women with CHD.

It has been recommended that post menopausal HRT should not be used to reduce risk of CHD events in women with CHD.[19]

Following the recommendations of the primary prevention trial (WHI) and the secondary prevention trial (HERS), a scientific review of all English language study identified in Medline (1966-2001). Heath STAR (1975-2001) and Cochrane library database was done by Heidi D and colleagues.[20] this review summarizes that the benefits of HRT include prevention of osteoporotic fractures, and colorectal cancer while prevention of dementia is uncertain. Harms include CHD, stroke, thromboembolic events, breast cancer, with 5 or more years of use, and cholecystitis. They conclude that use of HRT for primary prevention of chronic conditions requires re-evaluation by postmenopausal women and their physicians.

The following is American Heart Association Statement 2001[20]:

- Women without cardiovascular disease should base the decision to use HRT on non-coronary benefits & risks.
- Women with cardiovascular disease HRT should not be initiated for secondary prevention of cardiovascular disease.
- Women with cardiovascular disease and taking HRT base the decision to stop or continue HRT on non-coronary benefits and risks. Stop HRT after acute events, reinstitution should be based on non-coronary benefits and risks.

(Adapted from Mosca et al. according to the scientific statement of the American Heart Association).

The U.S. Preventive Service Task Force (USPSTF) based on evidence from several studies, summarizes the recommendations for HRT as follows.[21] Benefits include increased bone mineral density (good evidence), reduced risk of fracture (fair to good evidence) and reduced risk of colorectal cancer (fair evidence). Harms include increased risk of breast cancer (good evidence), venous thromboembolism (good evidence), coronary heart disease (fair to good evidence), stroke (fair evidence), cholecystitis (fair evidence). The task force found that the evidence was insufficient to assess the effects of HRT on other important outcomes, such as dementia and cognitive function, ovarian cancer, mortality from breast cancer or cardiovascular disease or all cancer mortality. The USPSTF did not evaluate the use of HRT to treat symptoms of menopause such as vasomotor symptoms (hot flashes) or urogenital symptoms. The USPSTF conclude that the harmful effects of oestrogen and progestin are likely to exceed the chronic disease prevention benefits in most women. The balance of benefits and harms for an individual woman will be influenced by her personal preferences, individual risks for specific chronic disease, and the presence of menopausal symptoms.

US Preventive Services Task Force Grades for Strength of Overall Evidence.

Grade	**Definition**
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of

evidence is limited by the number, quality or consistency of individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor — Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flows in their design or conduct, gaps in the chain of evidence or lack of information on important health outcomes.

V. Bone

It is well known that osteoporosis is more common in women than in men as a result of the bone loss that occurs with the menopause. Peak bone mass is reached in the forth decade of life and there is a progressive reduction thereafter with an accelerated loss following the cessation of ovarian function. Besides aging, other risk factors for osteoporosis include Caucasian race, smoking, excessive alcohol intake, renal disease, and immobilization and corticosteroid therapy. Oestrogen is considered to have antiresorptive effect on bone, also an anabolic effect of oestrogen on the skeleton have been suggested. Oestrogen receptors have been identified in the bone- forming osteoblasts. [23]

It has been said that the most important factors, which determine whether a woman will develop osteoporosis, are her maximum premenopausal skeletal mass, the peak bone density and the rate at which she subsequently loses bone. Systemic administration of appropriate oestrogen doses by oral preparations, transdermal patches or percutaneous implants can all significantly increase bone mineral density.[24, 25] It has also been confirmed that therapy reduces the incidence of osteoporotic fractures at both hip and spine. It has been estimated that if oestrogen therapy is maintained for five years, the incidence of osteoporotic fractures is reduced by 50-75% [26].

Alternative Therapies

Avoidance of risk factors and an adequate dietary intake of calcium and regular exercise are known to be beneficial for the prevention of osteoporosis. In observational trails exercise has been associated with decreased vasomotor symptoms. The biphosphonates are powerful antiresorptive agents which inhibit osteoclastic action and are believed to be beneficial to reduce vertebral fractures. [27] Calcitonins, Raloxefene and anabolic steroids are other options for the prevention and treatment of osteoporosis. [23, 28,29]

Soy has been shown to decrease vasomotor symptoms, lower lipid levels and increase bone density. Fish oil is helpful for secondary prevention of CHD. Various phytoestrogens are present in soy, but also in flaxseed oil, whole grains, fruits, and vegetables. They have antioxidant properties, and some studies demonstrated favourable effects on other CVD risk factors, and in animal and cell culture models of cancer. Much scientific research needs to be conducted before we can begin to make science-based dietary recommendations. Despite this, there is sufficient evidence to recommend consuming food sources rich in bioactive compounds. From a practical perspective, this translates to recommending a diet rich in a variety of fruits, vegetables, whole grains, legumes [30] It is not clear whether soy consumption causes a decrease in cardiovascular events or fracture. It has been said [31] that active living is a worthy alternative potent for health promotion, broader than hormones in its benefits, and is the more empowering and ethical route for women's long term health. Soy contains the isoflavone phytoestrogens, genistein and daidzein. These isoflavones are partial estrogen agonists in cell and animal models, but effects from dietary soy in humans are unclear. Study to see the effect of soy consumption on gonadotropin secretion and acute pituitary responses to gonadotropin-releasing hormone in women showed that soy consumption increased gonadotropin secretion and acute pituitary responses to gonadotropin-releasing hormone in women.[32] Dietary soy protein has been shown to have several beneficial effects on cardiovascular health. The best-documented effect is on plasma lipid and lipoprotein concentrations, with reductions of approximately 10% in LDL Cholesterol concentrations (somewhat greater for individuals with high pretreatment LDL cholesterol concentrations) and small increases in HDL cholesterol concentrations. It has been said that dietary soy protein improves flow-mediated arterial dilation of postmenopausal women but worsens that of men. [33]

Conclusion

Current state of evidence for the benefits and harms of HRT have been examined. Patient preferences as well as evidence are important to initiate and/or continue HRT. Benefits and harms need to be re-addressed periodically to apply newly published evidence and to reassess emerging risk, co-morbidities and need of individuals. More research into alternative therapies and putting knowledge into practice is a way forward.

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