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ESTABLISHING THE RISK RELATED TO HORMONE REPLACEMENT THERAPY AND CARDIOVASCULAR DISEASE IN WOMEN

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ABSTRACT

Hormone replacement therapy (HRT) will have a profound impact on the cardiovascular system in postmenopausal women, which is achieved by its effects on metabolic risk factors for coronary heart disease (CHD) and on arterial function. Observational studies of hormone replacement therapy are showing coronary heart disease benefit, whereas randomised clinical trials are showing coronary heart disease risk. Early harm may be caused by inappropriate high starting doses for the woman's age, which may cause transient increases in thrombogenesis and adverse vascular remodelling. Later benefit could result from oestrogen action on metabolic risk factors, as well as direct arterial effects reducing atherogenesis. Apart evidence from observational studies, the use of hormone therapy for the prevention of cardiovascular disease (CVD) among postmenopausal women is controversial. The recent completion of several randomised clinical trials examining the effects of hormone therapy on CVD are presenting an opportunity to provide a more precise estimate of the cardiovascular risks of hormone therapy.

KEYWORDS: Hormone Replacement Therapy, Cardiovascular vascular disease, Thrombogenesis, Risk assessment.

INTRODUCTION

Coronary heart disease (CHD) is the most common cause of death in women in the UK, northern European countries and North America, whereas stroke is more common in southern European countries.[3] CHD is uncommon in premenopausal women, especially nonsmokers,

but loss of ovarian function is associated with adverse metabolic changes and with increased incidence of CHD. The menopause is therefore an important CHD risk factor, unique to women. Hormone replacement therapy (HRT) is being used for more than 60 years to treat menopausal oestrogen deficiency and increase longevity in postmenopausal women.[1] But the effect of HRT on cardiovascular risk has been the subject of much debate. Numerous observational studies have shown the benefits of HRT on CHD, while some randomised controlled trials (RCTs) have demonstrated negligible effects.As there are clear biological effects of oestrogen on the cardiovascular system, with studies showing beneficial effects on classical risk factors for CHD (e.g. dyslipidaemia and insulin resistance, as well as arterial endothelial function), it seems unlikely that HRT should not benefit CHD in postmenopausal women.[4] But, it has been shown that inappropriately high doses of oestrogen may cause cardiovascular harm owing to transient disturbances in thrombogenesis and vascular remodelling. Almost all randomised studies using clinical outcomes failed to show benefits in older women. In these studies, the average starting age of the participants was mid-60s, and included inappropriately high doses of HRT. On par to that, there were trends to benefit women in the observational studies, comprising participants in their early 50s, the average onset age for menopause, in which appropriate dose of HRT was given.[8] In addition, a pilot study using older women on lower dose HRT did not demonstrate any cardiovascular harm. But benefits were shown in younger women on HRT early in the postmenopause, there may be similar benefits in older women with an appropriate low-dose therapy.

BIOLOGICAL BASIS FOR A ROLE OF ERT IN CVD

- ✓ Mendelsohn and Karas2 recently reviewed the physiological effects of estrogen on the cardiovascular system.
- ✓ Cardiovascular cells, as well as reproductive tissues, bone, liver, and brain, express both of the known estrogen receptors namely estrogen receptor a (ERa) and estrogen receptor b (ERb).[7]
- ✓ These receptors are important targets for endogenous estrogen, ERT, and pharmacological estrogen agonists.
- ✓ Estrogen–estrogen receptor complexes serve as transcription factors that promote gene expression with a wide range of vascular effects, including regulation of vasomotor tone and response to injury, that may be protective against development of atherosclerosis and ischemic diseases.

- ✓ Estrogen receptors in other tissues, such as the liver, may mediate both beneficial effects (eg: changes in apoprotein gene expression that improve lipid profiles) and adverse effects (eg, increases in gene expression of coagulation proteins and/or decreases in fibrinolytic proteins).[6]
- ✓ Two general estrogen-mediated vascular effects are recognized.
- ✓ Rapid, transient vasodilation occurs within a few minutes after estrogen exposure, independently of changes in gene expression.
- ✓ This rapid vasodilation appears to be due to the novel ERa –mediated activation of the endothelial nitric oxide synthase enzyme, but it is of unclear physiological significance.
- ✓ Progesterone and other hormonal receptors are also expressed in the vasculature, although their role in the development of CVD is poorly defined.[2]
- ✓ At present, the sum clinical impact of the genomic and nongenomic effects of ERT/HRT is unclear.
- ✓ As the molecular mechanisms responsible for the effects of estrogen are further elucidated, therapies may evolve which optimize the benefits of estrogen therapy while minimizing the risks.
- ✓ In addition to potentially beneficial vascular effects of ERT, well-established lipid alterations associated with oral ERT include favorable reductions in low-density lipoprotein (LDL) cholesterol and lipoprotein(a) and increases in highdensity lipoprotein (HDL) cholesterol.
- ✓ When ERT is combined with medroxyprogesterone acetate (MPA), there is initiation of the beneficial HDL-raising effect.[3]
- ✓ This is decreased when ERT is combined with natural progesterone.
- ✓ Oral ERT increases triglyceride levels 20%, although the clinical significance of this has not been established.
- ✓ The effects of ERT/HRT on several more recently recognized risk markers for CVD have been reviewed.

ROLE OF OESTROGEN

Oestrogen clearly has beneficial effects on the metabolic risk factors for CHD, as well as on arterial function.[5]

Changes in Lipids and Lipoproteins

Oestrogen reduces overall cholesterol levels and this effect is maintained for long term during treatment. This effect is considered to be beneficial in reducing the risk of CHD. It results primarily from a decrease in low density lipoprotein (LDL) cholesterol levels which will lead to an upregulation of apolipoprotein B_{100} ($apoB_{100}$) receptor.[1] Small density LDL particles are more readily cleared by scavenger mechanisms rather than by the $apoB_{100}$receptors, and are more likely to become embedded in the subendothelial space. Apart from increasing the level of small dense LDL particles, it also increases their clearance from the circulation. This may reduce the likelihood of their retention in the arterial wall. Small dense LDL particles may be more prone to oxidative damage, leading to foam cell production and eventual atheroma, however, oestrogen may protect LDL against oxidative damage.[6] Oestrogen also increases high density lipoprotein (HDL) cholesterol, particularly the HDL_2 subfraction. It inhibits hepatic lipase activity and increases the hepatic synthesis of apolipoprotein AI, the main protein component of HDL and HDL_2.

While the effects on LDL cholesterol levels are unaffected by the addition of progestogen, the increase in HDL cholesterol are reversed or greatly reduced with the addition of androgenic progestogens owing to an increase in hepatic lipase activity. The effects of HRT are clearly linked to the dose and route of administration, which determine its effects on triglycerides.[11] Oral oestrogen increases triglycerides, while this is reduced or reversed by the addition of androgenic progestogens. Conversely, transdermal oestradiol reduces triglycerides, which should reduce the risk of CHD.

Effect of Insulin resistance by tissues

The resistance of tissue to insulin action elevates the future risk of developing both CHD and type 2 diabetes mellitus. Oestrogen has beneficial effects on the metabolism of glucose and insulin, which results in a reduction in insulin resistance.[9]

Effect on Body fat

Central body fat accumulation is an important risk factor for CVD. There is a common misconception that HRT results in weight gain; but it has little effect on body weight. In fact, many women lose weight with HRT as gain weight. Central fat distribution is linked to insulin resistance and the metabolic syndrome and, therefore, is an increased risk for CHD[12]. At menopause there will be increase in central fat distribution, but HRT reverses the changes

in body fat distribution associated with menopause. This results in a reduction in central fat accumulation.[10]

THE EFFECTS OF OESTROGEN ON VASCULAR FUNCTION

Oestrogen has wide effects throughout the vasculature, including endothelial function.

On Vasodilation

- ✓ Oestrogen increases levels of endothelial nitric oxide synthase (eNOS) and subsequently increases the production of nitric oxide (NO) which is a potent vasodilator regulates blood pressure and platelet function, and inhibits vascular smooth muscle proliferation and the expression of adhesion molecules.[6]
- ✓ Oestrogen also reduces the release of endothelin-1, which is a potent vasoconstrictor. Oestrogen also reduces angiotensin-converting-enzyme activity, which benefits cardiovascular health.

On Vascular remodelling

The abnormal deposition and remodelling of vascular extracellular matrix are important processes involved in the pathogenesis and progression of atheroma. By normalising these processes atherogenesis can be inhibited.[3] The proteins called matrix metalloproteinases (MMPs) and their tissue inhibitors are central to vascular remodelling and may contribute to the development of cardiovascular disease. A study has shown that oestradiol increases the release of MMPs in a dose-dependent manner. Therefore, an increases in MMPs induced by low-dose oestrogen may normalise vascular remodelling, whereas high doses of oestrogen may produce large increases in MMPs and produce excessive remodelling. Therefore, the oestrogen dose at the onset of therapy will decide the beneficial or harmful effects on vascular remodelling.[13]

Renin-angiotensin-aldosterone system (RAAS)

Oestrogen plays a role in the renin-angiotensin-aldosterone (RAAS). Oral and transdermal HRT both contribute to a reduction in the activity of Angiotensin converting enzyme,that reduces the risk of CVD.[7] The progestogen drospirenone has antimineralocorticoid effects and also influences the RAAS by blocking the effects of aldosterone. HRT containing drospirenone therefore results in significant reductions in blood pressure in women with mild hypertension.

CLINICAL STUDIES OF HORMONE REPLACEMENT THERAPY ON CORONARY HEART DISEASE OUTCOMES

Observational studies consistently show a benefit of HRT on CHD, but some randomised studies do not agree with these findings.[4]

OBSERVATIONAL STUDIES

- Since 1983, many observational studies have shown a relational benefit between the use of postmenopausal HRT and a reduction in CHD.
- The biggest and most influential research from the Nurses' Health Study demonstrated a 40% reduction in CHD, and persisted for up to ten years.
- When the Nurses' Health Study supports a benefit from early initiation of therapy.[14]
- Women initiating HRT within ten years of menopause have a lower, non-significant, hazard ratio (0.54) for coronary disease.
- Furthermore, observational research has also demonstrated benefit in women with established CHD.
- However, there are concerns about observational studies owing to the non-randomisation to treatment. For example, women who choose HRT are healthier and less susceptible to CHD risk factors than those who do not take HRT[3].
- In this study of more than 91,000 women, those aged 60 years and under initiating HRT showed a significant 70% reduction in coronary death, while those aged over 60 years initiating HRT showed a non-significant reduction of 30%.

RANDOMISED TRIALS

- The Women's Health Initiative conducted a prospective Randomised Control Trails of Hormone Replacement Therapy, using either conjugated equine oestrogens alone or conjugated equine oestrogens with MPA in more than 27,000 (16,608 in the oestrogen plus MPA arm) postmenopausal women aged 50–79 years.[12] The study demonstrated no overall difference between treatments and placebo in outcomes of CHD. The study has subsequently been used as "evidence" that HRT does not lower the risk of CHD, however, there are problems with the results of this study. The study demonstrated some possible initial adverse cardiovascular effects, because of the high dose of oestrogen in the older women, but suggested benefit eventually.[9] This appeared to be greater in those women on oestrogen alone than on people with combined HRT, which suggests a possible adverse effect of MPA. Benefits were observed in women aged 50–59 years taking oestrogen alone. This was

statistically significant for a composite outcome of myocardial infarction, death and coronary interventions. With 13 years post-trial observational follow-up, the reduction in myocardial infarction in these oestrogen users became statistically significant compared with the placebo users.[1] No benefits were observed in women aged 70–79 years. The results suggested a "window of opportunity" to reduce the risk of CHD during the early postmenopausal years using HRT. Further analyses have shown that the CHD risk has not decreased in the first two years of treatment but a possible cardioprotective effect in women initiating oestrogen plus progestogen after six years, with decreasing the hazard ratio to half.[10] This age-dependency is supported by the findings of the Danish Osteoporosis Prevention Study (DOPS) in which women around the age of menopause were randomised to oral oestradiol, with or without cyclical norethisterone acetate (NETA), or no treatment for ten years, with a further six years observational follow-up.[6] This showed a significant reduction in a composite outcome of myocardial infarction, death or hospital admission for heart failure in the HRT users compared with placebo users. One limitation of the study was that the number of events was very small owing to the young age of the women involved – there were five myocardial infarctions in the randomised trial (one on HRT), which increased to 16 in the observational follow-up (five on HRT).[12]

The Heart and Estrogen/Progestin Replacement Study (HERS) included 2,763 postmenopausal women (aged 67 years on average) with established CHD to assess the impact of HRT on CHD events, particularly heart attack.[8] Participants were randomly assigned to an oestrogen/progestin combination or placebo, and treated for around four years. The study found that the use of oestrogen plus progestin in postmenopausal women with heart disease did not reduce the risk of heart attack. These results were different when compared to previous observational studies that found lower rates of CHD events in women with established CHD who underwent HRT. When the researchers examined the results by year, where they found that there was a trend towards a higher risk for "CHD events" (e.g. heart attack) during the first year of therapy.[9] This trend gradually declined over the course of the study. The majority of randomised trials with clinical cardiac end points have studied the effects of combined hormone therapies.

The Papworth HRT Atherosclerosis Survival Enquiry (PHASE) randomised trial considered the possible benefits of transdermal oestradiol or combined oestradiol/norethisterone in postmenopausal women with ischaemic heart disease.[7] The study analysed the results from

255 women, of whom 134 were treated with transdermal HRT and 121 acted as controls. The study found that treatment with transdermal oestrogen or combined oestrogen/progestogen did not reduce the incidence of acute CHD events (i.e. cardiac mortality, non-fatal myocardial infarction, or hospitalisation with unstable angina). In fact, the study suggested that the treatment could initially increase the incidence of these events by between 30% and 50%, although this was also followed by a decline in events.[13] In conclusion, the study recommended against the use of transdermal HRT for this purpose. Noting the trend towards early harm indicated by the PHASE study, and a possible later benefit suggested by the HERS trial, it was suggested that it may be appropriate for women already receiving HRT to continue. However, it should be noted that the dose of transdermal oestradiol (80mg) was inappropriately high for the age of the women.

The Kronos Early Estrogen Prevention Study (KEEPS) was another randomised study, involving more than 700 women. The main outcome findings have been presented but are yet to be published.[4] The main aim of the study was to compare low-dose oral oestrogen therapy with transdermal oestradiol, both with cyclical micronised progesterone in relation to atherosclerosis progression. Both therapy arms were compared with a placebo group. The average age of the participants was 52 years and they were all within three years of their final menstrual period.[3] Overall, the study found that no progression in atheroma was observed in either the treatment or placebo groups. The oral route provided increased benefits for mood, depressive symptoms, anxiety and tension for menopausal women compared with transdermal oestradiol. Low-dose oral oestrogen therapy also offered increased benefits for lowering LDL and increasing HDL cholesterol levels. Conversely, the KEEPS study suggested that the transdermal route offered greater reductions in insulin resistance and increased libido. In conclusion, the study suggested that overall outcome for HRT varies according to the individual, with advantages for transdermal therapy in some women, and advantages for oral in others.[10]

CONCLUSION

Numerous epidemiological observational studies indicate a beneficial effect when the treatment is started in the early postmenopause, including that of the WHI. In most countries, this is exactly the target age group for HRT use. It may be possible to develop HRT regimens around the time of menopause to reduce the risk of CHD in such women. Appropriate starting doses should ensure that any risks of stroke or VTE are minimised[13]. The observational

findings are supported by some, but not all. There is no firm support for the use of HRT solely for the prevention of CHD, but the evidence for HRT use in the primary prevention of CHD in postmenopausal women continues to accumulate. When given appropriately in terms of dose at initiation and types of hormones, HRT is not harmful to the cardiovascular system and may well prove to be beneficial.

Further clinical trials of different HRT types, doses and routes of administration are urgently needed. For example, the Royal Brompton and Harefield NHS Foundation Trust in the UK is currently sponsoring a study entitled OPTIMISE (Oral vs. Patch Trial in Menopause – Individualization of oeStrogEn therapy) to compare the effect of ultra-low-dose oral oestradiol/dydrogesterone combination versus a low dose transdermal therapy on the risks of Venous Thrombo Embolism and CHD.[9] Different metabolic effects of oral versus transdermal HRT administration routes may have different effects on CHD and VTE. Few studies have performed direct comparisons, and none have compared a transdermal regimen with a new ultra-low-dose oral oestradiol/dydrogesterone combination. Studies of the effects of newer HRT regimens (e.g. combinations of oestrogens classed as tissue selective receptor modulators [TSECs]) will also be needed.

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