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**ASSOCIATION OF HORMONE REPLACEMENT THERAPY IN POST
MENPOSALWOMEN AND CARDIOVASCULAR DISEASE**

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Abstract

Hormone replacement therapy (HRT) has a profound impact on the cardiovascular system in postmenopausal women, achieved through its effects on metabolic risk factors for coronary heart disease (CHD) and on arterial function. Observational studies have consistently shown an association between postmenopausal HRT use and a reduced incidence of CHD. However, the largest randomized trial initially reported no overall benefit on CHD risk. Subsequent analyses and follow-up of the study have demonstrated a significant benefit for CHD risk in healthy women initiating estrogen therapy soon after the onset of menopause. This benefit of early initiation of HRT has been confirmed in more recent trials. The dose and type of hormones at initiation of therapy appears crucial to obtaining CHD benefit.

Introduction

Hormone replacement therapy (HRT) has been used for more than 60 years to treat menopausal estrogen deficiency and increase longevity in postmenopausal women. However, following the publication of the Women's Health Initiative (WHI) study, the effect of HRT on cardiovascular risk has been the subject of much debate. The initial findings of this study demonstrated an increased risk of coronary heart disease (CHD) in older women, without increasing mortality. Numerous observational studies have shown the benefits of HRT on CHD, while some randomized controlled trials (RCTs) have demonstrated negligible effects. Since there are clear biological effects of estrogen on the cardiovascular system, with studies showing beneficial effects on classical risk factors for CHD (e.g. dyslipidemia and insulin resistance, as well as arterial endothelial function). It is interesting to note that almost all randomized 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. Conversely, there were trends to benefit women in the observational studies, comprising participants in their early 50s, the average onset age for menopause, who started on an appropriate dose of HRT. In addition, a pilot study using older women on lower dose HRT did not demonstrate any cardiovascular harm. While benefits seem to be shown in younger women on HRT early in the post menopause ^[1]

Material and methods

There was 3 different studies, the first one which is women's health initiative (WHI) conducted a prospective RCT of HRT, using either conjugated equine estrogen's alone or conjugated equine estrogen's with progesterone in more than 27,000 (16,608 in the estrogen plus progesterone) postmenopausal women aged 50–79 years. ^[2]

The second one which is 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, specifically heart attack. Participants were randomly assigned to an estrogen/progestin combination. ^[3]

The third and the last one Pap worth HRT Atherosclerosis Survival Enquiry (PHASE) randomized trial considered the possible benefits of transdermal estradiol or combined estradiol/norethisterone in postmenopausal women with ischemic heart disease. The study analysed the results from 255 women, of whom 134 were treated with transdermal HRT and 121 acted as controls. ^[4]

Results

The WHI 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. It demonstrated some possible initial adverse cardiovascular effects, perhaps owing to the high dose of estrogen in the older women, but suggested an eventual benefit. This appeared to be greater in those women on estrogen alone than in those on combined HRT, suggesting a possible adverse effect of progesterone. Benefits were seen in women aged 50–59 years taking estrogen alone. ^[2]

While HERS study found out that the use of estrogen plus progestin in postmenopausal women with heart disease did not reduce the risk of heart attack. These results were surprising given previous observational studies that found lower rates of CHD events in women with established CHD who undertook HRT. When the researchers examined the results by year, however, they found that there was a trend towards a higher risk for CHD “events” (e.g. heart attack) during the first year of therapy. This trend gradually declined over the course of the study. ^[3]

And PHASE study found that treatment with transdermal estrogen or combined estrogen/progestogen did not reduce the incidence of acute CHD events (i.e. cardiac mortality, non-fatal myocardial infarction, or hospitalization with unstable angina). In fact, the study suggested that the treatment could initially increase the incidence of these events by between 30% and 50%. ^[5]

Discussion

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. Furthermore, observational research has also demonstrated benefit in women with established CHD. Women who choose HRT are healthier and less susceptible to CHD risk factors than those who do not take HRT. The benefits and risks of HRT vary by dosage, regimen, and timing of initiation. Data accumulated from numerous studies have shown that, in women under the age of 60 years with symptoms or other indications, initiating HRT near their menopause provides a favorable benefit/risk ratio. Age and years since the menopause are now known to be important variables affecting the benefit/risk profile of HRT. Starting HRT less than 10 years since a woman's menopause has been shown to lead to a significant reduction in death and a reduction in CVD. There is a lower incidence of CVD in those women who take HRT within 10 years of their menopause.^[4]

Conclusion

The WHI had a major impact on the management of postmenopausal women. Following initial publication, prescribers and regulatory bodies disparaged the use of HRT. Subsequent data analysis has cast doubt on the initial interpretation of the results. Numerous epidemiological observational studies indicate a beneficial effect when the treatment is started in the early post menopause, 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.

Recommendations

Women should be informed that:

- HRT with estrogen alone is associated with no, or reduced, risk of coronary heart disease;
- HRT with estrogen and progestogen is associated with little or no increase in the risk of coronary heart disease;
- Taking HRT under 60 years does not increase a woman's risk of CVD;
- The presence of cardiovascular risk factors is not a contra-indication to HRT;
- It is essential to optimally manage any underlying cardiovascular risk factors (e.g. blood pressure, cholesterol).

References:

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