Cochrane review
Long-term hormone therapy for perimenopause and postmenopausal women
Marjoribanks 2017

Nearly all statistically significant findings described in this review derived from the two biggest studies - HERS 1998 and WHI 1998. Both studies evaluated oral conjugated equine oestrogen (CEE) 0.625 mg, with or without continuous methoxyprogesterone (MPA 2.5 mg). Smaller studies using other types of HT reported very few or no major clinical events. We were generally unable to combine results from individual studies because they used different types of HT, which may not be equivalent in effect, or they differed with respect to the study population, or both. Controversy surrounds the degree to which the findings of WHI 1998 apply to any type of HT other than continuous combined oral CEE 0.625 mg with or without MPA 2.5 mg. Effects may vary with different oestrogens and progestogens, different time frames for the use of HRT and different doses and routes of administration (e.g. unopposed oestrogen and intrauterine progestogen). Observational evidence shows that transdermal oestrogen differs from oral oestrogen in that it is not associated with increased risk of venous thromboembolism and suggests that some types of progestogen are thrombogenic but others are safe in this respect (Canonico 2007).

Most of the included studies had a mean participant age over 60 years, and none focused on perimenopausal women. In all but one of the 20 studies that reported mean participant age, mean age at enrolment was over 50 years. This does not reflect usual clinical practice with respect to prescribing of HT, which is most likely to occur for treatment of vasomotor symptoms at the time women reach menopause (Pedersen 2003). Moreover, participants described as 'relatively healthy' in this review were derived largely from WHI 1998. Investigators reported a high frequency of obesity and hypertensive disorders among WHI 1998 participants; only 30% were of normal weight, and 30% were morbidly obese (body mass index (BMI) > 30 kg/m2); 36% were receiving treatment for hypertension or had blood pressure exceeding 140/90 mmHg at enrolment.

Evidence is lacking on the long-term effects of HT on healthy younger women, who are most likely to use it for menopausal symptoms. Such women are likely to be in their early fifties, when the absolute risk of a life-threatening event is low; it has been estimated that absolute risk for many diseases approximately doubles with each decade of age (Hulley 2004). Subgroup analyses of women 50 to 59 years of age in WHI 1998 (combined HT arm) revealed that for relatively healthy women taking combined continuous HT, the only increase in risk that reached statistical significance was risk of venous thrombosis. Risk in the HT group increased from eight venous thromboses per 10,000 women per year to 19 per 10,000 women per year. This increase in risk was highest during the first year of therapy but continued over 5 years of treatment, and it was particularly high in obese women (i.e. women with a body mass index greater than 30), who had a 5-year risk of 1.4% compared with 0.5% among women of normal weight. In the oestrogen-only arm of WHI 1998, over the full 10.7 years of intervention and extended follow-up, younger women (aged 50 to 59 years) randomised to HT had significantly more favourable outcomes than those randomised to placebo. The HT group had significantly lower hazard ratios for coronary heart disease, myocardial infarction and death when compared with the placebo group. Findings were similar for both coronary outcomes when data were stratified by time since menopause rather than by age. This contrasted with findings in older women, among whom those in the HT group showed a trend for higher rates of coronary heart disease, myocardial infarction and death, and significantly higher rates of colorectal cancer and chronic disease. WHI 1998

authors noted that study participants took unopposed oestrogen for a median duration of less than 6 years, and that study results cannot be extrapolated to longer or shorter treatment durations. Moreover, it is important to note that oestrogen-only HT is contraindicated for women with an intact uterus, as use from 1 to 5 years has been estimated to increase the risk of endometrial cancer threefold (from a baseline lifetime risk of about 3% for a woman of 50), with effects persisting for several years after oestrogen is stopped (Grady 1995).

Summary

Cardiovascular disease

No evidence indicates that hormone therapy (HT) has a role in the treatment or prevention of cardiovascular disease. On the contrary, HT significantly increases the incidence of stroke and venous thromboembolism. and combined continuous HT also significantly increases the risk of coronary events (myocardial infarction or cardiac death). Oestrogen-only HT does not appear to have any statistically significant effect (positive or negative) on coronary disease.

It has been suggested that vascular effects of HT may differ according to a woman's age or time since onset of menopause. Thus oestrogen may counteract the early stages of atherosclerosis in recently menopausal women by inhibiting lipid deposits within the endothelium. However, HT may have adverse effects on more advanced disease, by facilitating an increase in enzymes that tend to disrupt atherosclerotic lesions, and by encouraging clot formation (Manson 2013; Reslan 2012). Research findings on the effect of HT in early menopause on intermediate outcomes of CVD are variable (ELITE 2014; KEEPS 2012), and research findings on this topic are continuing (Manson 2015).

Breast cancer

In WHI 1998 (combined HT arm), breast cancer rates in the HT group were initially lower than in the placebo group, and when WHI 1998 and WISDOM 2007 data were combined, at 1 year's follow-up, the difference reached statistical significance, favouring the intervention group. However, by the fourth year of use, more events occurred in the HT group, and a statistically significant trend showed increasing risk over time. At a mean of 11 years' follow-up in WHI 1998, women in the combined HT group had a significantly higher rate of invasive breast cancer than controls, and longer follow-up (to a median of 13.2 years) showed no evidence of attenuation of risk (Chlebowski 2015a). At 11 years, the trend toward a higher rate of death from breast cancer approached statistical significance (Chlebowski 2010). This long-term increase in risk was apparent despite evidence that the risk of breast cancer associated with combined HT declined markedly over the first 2 years after discontinuation of hormones (Chlebowski 2009a).

WHI 1998 reported a decrease in the risk of breast cancer in the unopposed oestrogen arm of the trial, which reached statistical significance when investigators took into account the entire 10.7 years of intervention and extended follow-up. Cumulative event rates still differed significantly between groups over 13 years' follow-up, and risk of death from breast cancer was lower in the HT group at nearly 12 years. Comparison of hazard ratios during early and late post-intervention periods showed that lower risk of breast cancer in the oestrogen arm persisted for about 4.5 years after the intervention was provided, at which point a significant difference between the interventions was no longer evident (Chlebowski 2015a; Chlebowski 2015b). Subgroup analyses showed significantly fewer early cancers and significantly fewer ductal carcinomas in the intervention group, although the incidence of lobular tumours did not differ significantly. Results showed that the reduction in breast

cancer risk was concentrated in women without benign breast disease (P = 0.01) or a first-degree family history of breast cancer (P = 0.02) (Anderson 2012). Oestrogen-only HT appears to increase the number of women needing repeat mammography or breast biopsy but (in contrast to combined HT) does not appear to substantially compromise breast cancer detection (Chlebowski 2010a).

Colorectal cancer

The significantly reduced incidence of colorectal cancer in women taking combined continuous HT in WHI 1998 was offset by the finding that colorectal cancers diagnosed in such women tended to be more advanced, with greater likelihood of lymphatic or metastatic involvement.

Lung cancer

Post hoc analysis of WHI 1998 data revealed that combined HT did not significantly increase the incidence of lung cancer over 8 years' follow-up but did increase mortality from lung cancer, independent of smoking status. Study authors (Chlebowski 2009) suggested that this might be so because combined HT stimulates the growth of preexisting small cell lung cancers.

Gynaecological cancers

Endometrial cancer

None of the included studies showed an increase in the incidence of endometrial cancer in the group taking HT. Three studies randomised women with a uterus to oestrogen-only HT (EPAT 2001; ESPRIT 2002; PEPI 1995). As endometrial cancer is well documented as an adverse effect of unopposed oestrogen (Kurman 1985), these women were closely monitored for atypical endometrial hyperplasia and received treatment (and discontinuation of study medications) if it was detected. PEPI 1995 reported that women in the oestrogen-only HT group were significantly more likely to develop atypical endometrial hyperplasia than women in the placebo group, whereas women in the combined HT groups in the same study showed no increased risk of hyperplasia. After more than 13 years' extended follow-up, rates of endometrial cancer were lower in the combined HT group in WHI 1998.

Ovarian cancer

A randomised study with 4-year follow-up of 130 women with a history of ovarian cancer (Guidozzi 1999) found that oestrogen-only hormone therapy did not negatively affect disease-free or overall survival time compared with no hormone therapy. A similar randomised study (AHT 2015) showed that women with severe menopausal symptoms after ovarian cancer who took HT (of varying types, according to consultant preference) had improved overall and relapse-free survival compared with controls not taking HT. The present systematic review did not include these studies because they lacked a placebo control group.

Hip fracture

Our analyses of hip fracture may have had insufficient power to reach conclusive findings. The risk of hip fracture rises steeply from the age of about 60 years but is still under 0.5% among women in the UK 65 to 69 years of age (Banks 2009).

Women with a history of breast cancer

HT appears to carry increased risk of recurrence for women with a history of breast cancer. Two unblinded studies conducted in Sweden randomised breast cancer survivors with menopausal symptoms to HT or non-hormonal treatment. Both studies were terminated early owing to a statistically significant increase in the incidence of recurrent breast cancer in the hormonal group in one of the studies (risk ratio (RR) 3.5, 95% confidence interval (CI) 1.5 to 8.1) (Chlebowski 2004; Holmberg 2004). After a median of 4 years' follow-up in this study, a clinically and statistically significantly increased risk of a new breast cancer event continued in the HT arm (RR 2.4, 95% CI 1.3 to 4.2) (Holmberg 2008). A similar study initiated in the UK terminated recruitment prematurely in January 2004 (ICR 2001).

Authors' conclusions

Implications for practice

HT for women with menopausal symptoms

Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harm arising from short-term use of low-dose HT, provided they do not have specific contraindications. HT may be unsuitable for some women, including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease (e.g. obesity, history of venous thrombosis) or increased risk of some types of cancer (e.g. breast cancer in women with a uterus). The risk of endometrial cancer among women with a uterus taking oestrogen-only HT is well documented. Although none of the studies included in this review focused specifically on women in the age group most likely to require menopausal symptom relief, subgroup analyses in WHI 1998 suggested that among relatively healthy women in their 50s taking oestrogen-only or combined HT, the only significant risk was increased incidence of venous thromboembolism in those taking combined HT. Absolute risk of venous thromboembolism was low, at 0.5% overall for a woman taking HT for 5 years. For women in their 50s without a uterus, taking oestrogen-only HT for 5 to 6 years appears relatively safe and may even confer some health benefits. However, safety over longer-term use is unknown.

HT for other indications

HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women. Although HT is considered effective for prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-oestrogen therapies are unsuitable. Strong evidence suggests that both oestrogen-only HT and combined therapy significantly increase the risk of stroke and gallbladder disease, and that long-term use of combined continuous therapy also increases the risk of coronary events, breast cancer, death from lung cancer and (in women over 65 years of age) dementia.

HT for women with previous disease or smoking history

HT is not recommended for use in women with cardiovascular disease or with a history of venous thrombosis or breast cancer. Randomised evidence provides no specific contraindications for its use in women with a history of endometrial cancer or ovarian cancer, although data are scanty. Women at high risk of lung cancer (current smokers or long-term past smokers) should be aware that combined HT increases the risk of death from lung cancer.

Implications for research

No studies have adequately assessed the safety of HT used for symptom relief by perimenopausal women, women younger than 50 years or women with temporary or permanent iatrogenic ovarian failure. Not enough is known about factors that may modulate the risks involved, such as clinical characteristics or biomarkers affecting individual women, different oestrogens and progestogens, different time frames for the use of HT and different doses and routes of administration (e.g. unopposed oestrogen and intrauterine progestogen, whether the risk of thromboembolism is diminished by the use of patches). Reliable evidence is needed to show the efficacy and safety of alternatives to HT for control of menopausal symptoms among women who may wish to avoid using HT, or for whom its use is unsuitable.