BJOG: an International Journal of Obstetrics and Gynaecology
June 2005, Vol. 112, pp. 692–695
DOI: 10.1111/j.1471-0528.2005.00541.x

REVIEW

Current evidence about the effect of hormone replacement therapy on the incidence of major conditions in postmenopausal women

The last few years have seen an astonishing growth in the availability of unbiased information about the effects of hormone replacement therapy (HRT) on the risk of major illnesses developing in postmenopausal women. Two years ago we reviewed the evidence that was then available from four randomised controlled trials,[1–5] but now results from a further five trials have been published.[6–10] The largest and most influential trials are the two arms of Women's Health Initiative (WHI), set up specifically to investigate whether use of HRT reduced the incidence of coronary heart disease in otherwise healthy women.[11] It randomised 10,739 women who had had a hysterectomy to placebo or 0.625 mg equine oestrogen[10] and 16,608 women who had not had a hysterectomy to placebo or 0.625 mg equine oestrogen and 2.5 mg medroxyprogesterone acetate.[5]

The WISDOM trial, based in the UK with a similar design to the US-based WHI, was closed in October 2002.[12] No other large randomised controlled trial of the effects of HRT is now in progress, and so it is timely to review what has been learned — as well as what cannot be learned — from the trials.

Evidence from randomised controlled trials

Figure 1 summarises the main results from the eight randomised controlled trials designed with cardiovascular disease as the primary outcome.[2–8,10] The findings from three trials,[4,7,10] where the active treatment was oestrogen-only HRT, are combined together, as are the findings from five trials[2,3,5,6,8] where the active treatment was generally oestrogen–progestogen (i.e. combined HRT).

Overall, the trials found no significant difference in coronary heart disease incidence between women in the placebo and the oestrogen-only or oestrogen–progestogen groups: the relative risk combining together results from all eight trials is 1.05 (95% CI 0.94–1.17), based on 1200 coronary events (similar to the overall findings from smaller trials, set up mainly to investigate the effect of HRT on menopausal symptoms).[13] For stroke, there was a statistically significant increased risk associated both with use of oestrogen-only and with use of combined HRT, compared with placebo. The overall relative risk of stroke in HRT users compared with non-users, based on almost 800 events in all eight trials combined, is 1.31 (95% CI 1.13–1.52). There were only about 200 pulmonary embolic events in total, and the overall relative risk was significantly elevated, at 1.72 (95% CI 1.30–2.28), with no significant difference between the results for oestrogen-only and combined HRT. Both for coronary heart disease and for venous thromboembolism, there is some evidence that the relative risks are greater in the first year after randomisation than subsequently.[2,5,7,10]

The trials also found a significantly decreased incidence of hip fracture, with no significant difference in the magnitude of the protection conferred by oestrogen-only or combined HRT. The overall relative risk, based on about 250 events in all eight trials, is 0.67 (95% CI 0.53–0.86).

The results for cancer are based on about 600 incident breast cancers and 250 incident colorectal cancers. By contrast to cardiovascular disease and fracture, the findings for each type of cancer differ significantly between the trials using oestrogen-only and those using oestrogen–progestogen HRT — with a significantly greater relative risk of breast cancer for combined than oestrogen-only HRT ($P = 0.004$), and a lower relative risk of colorectal cancer for combined than oestrogen-only HRT (of borderline significance, $P = 0.04$).

Results published recently from the ninth randomised controlled trial, the Swedish-based HABITS trial (Hormone replacement therapy after breast cancer — is it safe?), are not included in the figure, as breast cancer was its main outcome and the study population was women who had already been diagnosed with breast cancer.[9] The trial was stopped early because of an increased incidence of local recurrence, distant metastases and contralateral breast cancer in the HRT groups (relative risk = 3.5, 95% CI 1.5–8.1, for HRT *vs* no HRT, based on 34 events).

Strengths and limitations of randomised controlled trials

By far the greatest strength of the randomised controlled trials is that, because allocation of HRT is at random, the findings are unlikely to be biased. This is particularly relevant for coronary heart disease, where prescribing of HRT is influenced by past health, such that women with a history of diabetes and other conditions that predispose to coronary

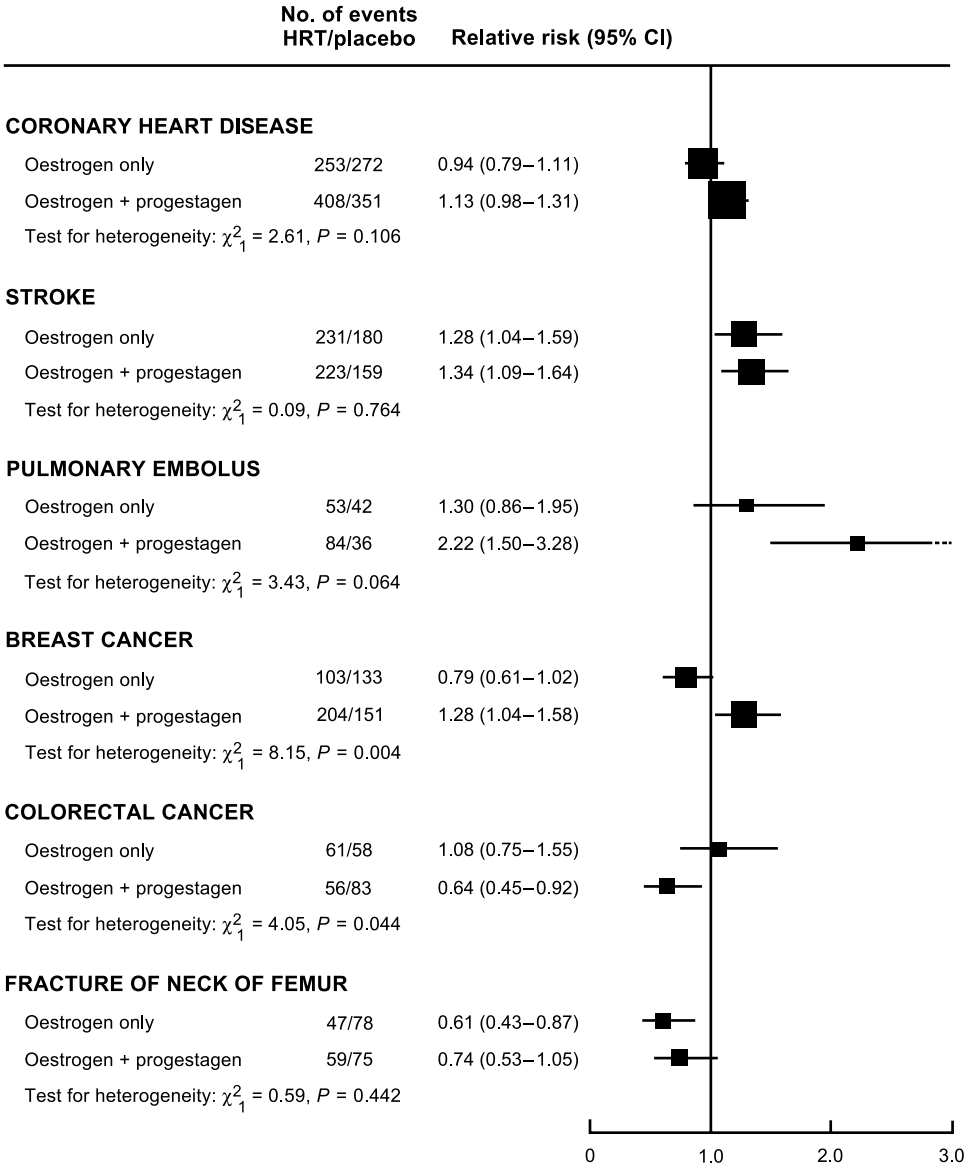

Fig 1. Summary of results from randomised controlled trials of oestrogen-only HRT *versus* placebo[4,7,10] and combined oestrogen–progestogen HRT *versus* placebo.[2,3,5,6,8]

heart disease are less likely to be prescribed HRT than are women without such illnesses.[14,15] This type of differential prescribing was evident in the late 1990s in the UK[15] even though it was widely believed that use of HRT protected against coronary heart disease. Such differential prescribing can seriously distort comparisons of coronary heart disease rates between HRT users and non-users in observational studies and statistical adjustments cannot overcome this type of bias.[11,14,16] Randomised controlled trials must therefore be relied upon to provide unbiased information about the effect of HRT on coronary heart disease.

Six of the randomised controlled trials were set up with coronary heart disease as the chief outcome.[2,5–8,10] The size of each was determined by the expected number of coronary events. While the trials offer the theoretical advantage of unbiased results for other outcomes they are compromised by the comparative infrequency of other serious conditions, and thus, by random error. Differential prescribing is less of a problem for most of the other conditions of interest, such as thromboembolic disease, fracture and cancer, as their incidence is less readily predicted by known medical conditions than is coronary heart disease, and so the potential for bias in observational data is not so severe.

Another problem when interpreting the evidence from randomised controlled trials is the dilution of effects resulting from poor compliance, particularly relevant in the WHI.[5,10] As well, by far the most common HRT used in the trials was equine oestrogen with or without medroxyprogesterone acetate,[2,5,8,10] and so randomised evidence on the effects of other types of HRT is extremely limited. Answers to questions about the effects of different types

Table 1. Relative risk of breast cancer,* according to body mass index, in the Million Women Study and the distribution of body mass index among HRT users in the Million Women Study and in the WHI trial.[10]

Body mass index (kg/m^2)	Relative risk (95%CI)*	Percent of HRT users in each category of body mass index (%)	
		Million Women Study (UK)[20]	WHI (USA)[10]
<25	1.36 (1.14–1.63)	45	21
25–29	1.14 (0.94–1.40)	37	34
≥30	0.99 (0.73–1.34)	18	45

* Relative risk of breast cancer in women who reported that they were current users of oestrogen-only HRT at recruitment into the Million Women Study,[20] compared with never users, for women using oestrogen-only HRT for a similar average duration to that of women in the WHI Trial of oestrogen-only HRT.

and of different patterns of use of HRT on a range of conditions will therefore not be available from the trials and will necessitate the judicious analysis and interpretation of observational data.

The totality of the evidence

Results from all randomised controlled trials, taken together, have reliably excluded the possibility that use of equine oestrogen with or without medroxprogesterone acetate substantially protects against coronary heart disease. This is the main question that the trials set out to answer. The trials have also shown that use of these preparations increases the risk of stroke and also of venous thromboembolism. However, the trials are too small to permit meaningful comparison of the effects of different types of HRT on cardiovascular disease: for example, it is not possible to know, with any certainty, whether or not oestrogen-only and combined HRT have different effects on these conditions.

The randomised controlled trials have confirmed results from observational studies showing that use of HRT protects against fracture in general, and hip fracture in particular. While the trials do not have sufficient power for reliable comparison between the effects of oestrogen-only and combined HRT or between the effects of specific HRT preparations, results from large observational studies show that most of the commonly used HRT preparations confer a similar degree of protection against fracture.[17]

Use of oestrogen-only HRT increases the risk of endometrial cancer, and use of oestrogen–progestogen combinations substantially attenuates that increase in risk.[18] The evidence about HRT and endometrial cancer comes solely from observational studies.

There is a large body of observational data showing that current users of HRT are at an increased risk of breast cancer, and that the risk is substantially greater for combined oestrogen–progestogen than for oestrogen-only HRT, the risk increasing with increasing duration of use.[19,20] Results from randomised controlled trials show a significantly increased risk with combined HRT and a significantly greater effect for combined than for oestrogen-only HRT, in agreement with the findings from observational studies. The relative risk of 0.79 shown in the figure for oestrogen-only HRT has wide 95% confidence intervals, ranging from 0.61 to 1.02, and is largely influenced by the WHI trial results.[10] As shown in the accompanying table, 45% of the HRT users in the WHI were obese, with a body mass index of greater than 30 kg/m^2. Use of HRT has been shown to have a lesser effect on the relative risk of breast cancer in obese than in thinner women[19,20] and the results for obese women in the observational studies do not substantially conflict with the trial results (see Table 1). For other cancers, the trial results are prone to even greater random error than for breast cancer, and the possibility that combined HRT offers greater protection against colorectal cancer than oestrogen-only HRT needs further investigation.

Applicability of the findings from trials to the general population and advice from independent regulatory bodies about prescribing HRT

Most of the randomised controlled trials were conducted in the USA, on selected populations, using specific types of HRT. Questions inevitably arise about whether trial results can be generalised to other populations and to other HRT preparations. The main way these questions can be addressed is to see if the findings vary across different subgroups of women, namely, those of different ages, with different medical histories, different lifestyles, and so forth, and across women using different preparations. The replication of results across studies of different designs and in different settings also helps address such questions (provided, of course, that their designs allow unbiased comparisons).

The WHI recruited women aged 50 to 79 years and, after the trial results were published, some have expressed concern that HRT might have different effects on coronary heart disease in women of different ages: however, there was no prior hypothesis to this effect, nor were there any statistically significant variations in the trial results, according to women's ages at recruitment.[10,11,21] The only definite evidence of variation in the effect of HRT between women is for breast cancer, where the relative risks associated with the use of HRT are lower in obese than in thinner women.[19,20] Because women in the UK are not as obese as in the USA (Table 1), results on the relation between HRT and breast cancer from the USA may not be directly applicable in the UK, or indeed in the rest of Europe.

So far the only firm evidence of different effects by different types of HRT is for breast cancer and endometrial cancer (see Fig. 1).[18,20] For most of the other major

conditions, it is unclear whether the effects vary by type of HRT or by its mode of administration, or whether the effects vary between women. Nevertheless, the availability of considerably more reliable evidence than existed a few years ago means that prescribing of HRT can now be guided by that evidence.

Independent regulatory bodies in the UK,[22] the European Union[23] and the USA[24] give broadly similar advice: use HRT only for menopausal symptoms and for as short a time as possible. Recently the Royal College of Obstetricians and Gynaecologists have echoed these recommendations.[25] These bodies acknowledge that prescribing decisions are not simple, and that each woman's personal circumstances and medical history needs careful evaluation at regular intervals. The Committee on Safety of Medicines[22] also provides estimates of absolute risk, to assist with these decisions (quoted by Lumsden, in an accompanying editorial).[26] Because HRT protects against fracture, but increases the risk of breast cancer, stroke and venous thromboembolism, each woman needs to consider the importance she attaches to each condition, as well as her personal circumstances and the severity of her menopausal symptoms.

Conflict of interest statement

Our research is funded by the cancer charity, Cancer Research UK, and by the Medical Research Council. The authors have not accepted honoraria from the pharmaceutical industry.

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