Hormone replacement therapy and breast cancer, endometrial cancer and cardiovascular disease: risks and benefits

MARIA K GODDARD

SUMMARY. The relatively restricted use of hormone replacement therapy in the United Kingdom has frequently been noted. It is possible that low prescribing rates may, in part, be due to the difficulty in interpreting the wealth of research evidence relating to the risks and benefits of hormone replacement therapy. Conflicting conclusions from research can cause considerable uncertainty and confusion. This paper reviews the evidence relating to hormone replacement therapy and the risks of breast cancer, endometrial cancer and cardiovascular disease and discusses the issues which require critical assessment. This should add to the information base available to general practitioners and thus assist in decision-making in the context of uncertainty.

Keywords: Hormone replacement therapy; menopause; subject reviews.

Introduction

THE relatively limited use of hormone replacement therapy for menopausal women in the United Kingdom compared with the United States of America and some other European countries, has been noted in the medical literature[1] and also in the mass media and women's press. Even among those who are at medium or high risk of cardiovascular disease and osteoporosis, such as those with bilateral oophorectomy or hysterectomy, the use of hormone replacement therapy is reported to be low.[2]

Although patient-initiated demand and interest appears to be strong,[3] the high expectations of hormone replacement therapy held by women may be tempered by their confusion and lack of knowledge about the relative risks and benefits associated with the therapy.[4,5] This may explain relatively poor compliance rates in practice[4] and the reluctance of women to take hormone replacement therapy prophylactically for osteoporosis when they are experiencing no adverse symptoms of the menopause.[6,7] Similarly, both in the UK and the USA, conservative prescribing behaviour by physicians has been attributed, in part at least, to uncertainty about the importance of the risks and benefits of the use of hormone replacement therapy.[8,9]

A recent study of general practitioners in Yorkshire concluded that knowledge of the risks and benefits of hormone replacement therapy was patchy, and many general practitioners indicated their views were strongly influenced by 'intuition and general philosophical considerations, rather than a formal appraisal of likely risks versus benefits'.[9] The same study also noted that a number of general practitioners showed limited knowledge of the current literature, and that the provision of more information about hormone replacement therapy could improve their ability to form opinions about the desirability or otherwise of hormone replacement therapy. This paper aims to review the evidence relating to hormone replacement therapy and the relative risk of breast cancer, endometrial cancer and cardiovascular disease and to discuss the issues which require critical assessment in the interpretation of the wealth of information currently available.

M K Goddard, BA, MSc, research fellow, Centre for Health Economics, University of York.
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Review of the research

Given the current status of epidemiological and medical knowledge about the side effects of hormone replacement therapy, and also the limitations inherent in the design of many of the trials undertaken to date, it is impossible to give an unequivocal answer regarding the desirability of prescribing hormone replacement therapy.

The effectiveness of hormone replacement therapy in ameliorating menopausal symptoms is not considered here. Similarly, the evidence relating to the potential effects of hormone replacement therapy on ovarian cancer and thromboembolic disease is not considered as it is still emerging. There is debate relating to longer term use of prophylactic hormone replacement therapy for osteoporosis in order to prevent or delay bone loss, and thus reduce the subsequent incidence of fractures. Although this is an important issue, especially in relation to current developments in screening for osteoporosis, it is not considered further in this paper as the potential beneficial effects of oestrogens on osteoporosis seem to be appreciated by the majority of general practitioners.[9] However, it is acknowledged that controversy remains — the size of the effect on fractures and the required duration and dose of hormone replacement therapy is still debated, as are the economic consequences of osteoporosis prophylaxis. Further discussion of osteoporosis can be found elsewhere.[10-12] These aspects of hormone replacement therapy use are probably causing less uncertainty and confusion than the risks related to cardiovascular disease, breast cancer and endometrial cancer and a review of the research relating to these three risks is presented here.

For some diseases, there is a wide range of estimates of potential effects. The following areas may be useful to consider when assessing the validity of results of research.

Study design

Owing to the long latency period for the development of many of the relevant conditions associated with hormone replacement therapy, the majority of studies use a case control design. The comparability of the controls is an important feature, and the adjustment of the estimates of relative risk for possible confounding variables is vital, although in practice this may prove to be difficult.

While some studies report results that are adjusted for potential biases relating to differences in characteristics between the comparison groups, others do not. The importance of this can be appreciated by considering that those with previous histories of breast cancer or heart disease, or those at high risk of these, are less likely to have hormone replacement therapy prescribed

anyway and this feature would bias the results if it was ignored. Likewise, previous use of oral contraceptive oestrogens, which may influence the risks of breast cancer and heart disease should be considered. For cardiovascular disease, the type of menopause (natural or surgical) and its age of onset can also influence risk of disease[13,14] as well as other lifestyle habits, such as smoking.

Type of hormone replacement therapy

The majority of research has focused on the use of unopposed oestrogens. However, unopposed oestrogens are now used mainly for women having no uterus. More recent moves have been made towards combined therapy (oestrogens and progestogen) for women with an intact uterus, in order to counteract the potentially adverse effects of oestrogen on the uterus,[15] which may cause endometrial cancer. Limited data relating to the potential effects of progestogen on breast cancer, heart disease and other disease are also available. The large UK study of hormone replacement therapy use[16] recognized that many women had received inadequately opposed therapy which would not be prescribed today.

New forms of therapy and modes of administration are constantly being introduced, for example, implants, transdermal systems (or 'patches'), and more recently, vaginal administration of oestrogen in tablet form which then turns to a gel. Thus, it is difficult to extrapolate from studies which consider mainly oral therapy to other, more recent approaches. The importance of this is illustrated in the case of cardiovascular disease, where it has been suggested that the addition of progestogen may negate the protective effect that unopposed oestrogen therapy is thought to have with respect to cardiovascular disease.[17] Similarly, it has also been suggested that the favourable effects of oral oestrogens on cardiovascular disease may be limited if oestrogens are delivered transdermally.[18,19] However, oestradiol implants may have the same protective effects as oral oestrogens.[20]

Duration of therapy

Some studies, especially where the data collected relate to either the USA, or to the 1970s and early 1980s, provide information about prescription patterns which are not appropriate to the UK in the 1990s.

The evidence shows that for some diseases there may be important links between risks and duration of use, longer use usually being associated with an elevated risk of adverse effects of therapy. In the UK, where general practitioners tend to err on the side of caution and prescribe fairly short courses of therapy,[2,9] some of the longer term adverse effects reported in the literature may not be applicable. Establishing the duration of use has proved difficult in practice, with concerns that some studies underestimate total duration by failing to define the baseline prescription status carefully,[21,22] and with the discovery of discrepancies between data on duration of use as recorded in pharmacy records, and that reported by women themselves. Lower dose courses have rarely been considered in the literature but are now receiving increasing attention in practice.

Breast cancer

The evidence concerning relative risk of hormone replacement therapy users versus non-users (where 'no use' = 1.0) in relation to breast cancer is shown in Table 1. Many studies have found an elevated risk of developing breast cancer for users of oestrogens. The estimates of relative risk vary widely but in general it appears that longer term use or higher doses are associated with increased risks, but it should be noted that the elevated risks reach statistical significance only in a small number of studies. Indeed, only in two cases do the elevated relative risks overall for women ever having used hormone replacement therapy reach statistical significance.[16,24] The Swedish study by Bergkvist and colleagues[33] has attracted much attention owing to the discovery of a large, but not statistically significant, relative risk of 4.4. associated with use of combined therapy, and a relative risk of 1.7 (statistically significant) for any type of oestrogen use of nine years duration or over. However, many of the methodological flaws outlined earlier, for example, failure to adjust for previous use of oral contraceptives and failure to ensure baseline status was defined adequately, have been noted in relation to this study and thus the results should be treated with caution.

On the contrary, Gambrell and colleagues[26] found a significantly reduced risk for users of combined oestrogens and progestogen compared with the non-users but there are also methodological flaws associated with this study. In particular, there were small numbers in the sub-groups, and the medical history was not investigated of all women in both groups to allow for bias owing to familial history of breast cancer. Therefore, it remains only suggestive until future research relating to combined therapy provides more evidence.

Table 1 also illustrates the importance of ovarian and uterine status. Women who have undergone a bilateral oophorectomy are at lower risk of breast cancer than those who have undergone natural or surgical menopause (with at least one ovary intact),[35] and thus even if hormone replacement therapy raises the risk, those with no ovaries may not experience a greatly elevated risk relative to non-users in general. The distinction between current and past use is also important. These complex relationships have been explored in more detail in both British and American studies.[16,25]

Overall, a small elevated risk for particular types of therapy over certain periods of time is apparent, especially for current use, but the validity of generalizing from these studies to current practice is doubtful and more evidence is needed.

Endometrial cancer

An increased risk of endometrial cancer associated with unopposed therapy is better documented and thus less controversial than for breast cancer. Table 2 illustrates that much of the available research regarding oestrogen-only therapy has also found a positive relationship between duration and risk and, to a lesser extent, dose and risk. The importance of choice of a control group has been debated in detail[42] as the possibility of detection bias arises since oestrogens may provoke uterine bleeding in women with previously asymptomatic endometrial cancer. As a result, increased diagnostic testing would occur, subsequently increasing the detection rate for this group. Some studies[43,50] have used several control groups for this reason and the possibility of underestimation of risk owing to surveillance bias has also been addressed in the literature.[54,56] However, the true risks probably lie somewhere midway between estimates that have, and have not, been adjusted for such biases. Indeed, the British Gynaecological Cancer Group concluded that such biases could account for only a small part of the observed association.[57]

The issue which seems more controversial is the role of progestogen in combined therapy. Progestogen has been shown clinically to prevent hyperplasia,[58] and in premenopausal women taking a combined oral contraceptive, the risk of endometrial cancer is decreased.[59] The number of studies considering combined therapy has been limited, but available research seems to suggest a protective effect from the addition of progestogen.[60,61] The UK cohort study, however, found that eight out of 14 women having endometrial cancer had taken

Table 1. Studies of hormone replacement therapy (HRT) and breast cancer published since 1980.

First author (date of publication)	No. of: Cases	Controls	Duration of use, total accumulated dose, daily dose or type of HRT or user status[a]	Relative risk (where 'no use' = 1.0) Overall	At least one intact ovary	No ovaries
Ross (1980)[23]	138	281	Ever	1.1	1.4	0.8
			1–1499 mg	0.8	0.9	0.9
			1500+ mg	1.9	2.5*	0.7
Hoover (1981)[24]	345	611	Ever	1.4*	1.5	1.3
			⩽4 yr	1.4	–	–
			5+ yr	1.7*	–	–
			1.25+ mg	1.8*	–	–
					Hospital Community	
Hulka (1982)[25]	199	451 Hospital	Ever	–	1.8 1.7	1.3
			0.5–3 yr	–	2.1 2.6	–
			4–9 yr	–	1.5 1.6	–
			10+ yr	–	1.7 0.7	–
		852 Community	⩽0.625 mg	–	1.9 0.8	–
			0.625+ mg	–	1.0 0.8	–
Gambrell (1983)[26]	53	Survey rates	Oestrogens	0.7	–	–
			Oestrogen and progestogen	0.3*	–	–
					Natural Surgical	
Kaufman (1984)[27]	1610	1606	Ever	0.9	– –	0.7
			<1 yr	–	0.9 1.3	0.4
			1–4 yr	–	0.9 1.2	0.8
			5–9 yr	–	0.7 0.7	1.1
			10+ yr	–	1.3 0.3	0.5
			<1.25 mg	–	1.2 0.7	2.0
			1.25+ mg	–	0.7 0.4	0.5
Hiatt (1984)[28]	119	119	Ever	–	–	0.7
			3+ yr	–	–	1.8
				Caucasian Japanese		
Nomura (1986)[29]	341	340	Ever	0.9 1.1	–	–
			<1 yr	0.9 2.4*	–	–
			1–5 yr	0.7 0.7	–	–
			6+ yr	1.3 1.9	–	–
					Natural Surgical	
Brinton (1986)[30]	1960	2258	Ever	1.0	1.1 1.0	1.1
			<5 yr	0.9	1.0 0.8	1.0
			5–9 yr	1.1	1.1 1.2	1.2
			10–14 yr	1.3	1.3 1.2	1.6
			15+ yr	1.2	1.7* 1.3	1.4
			20+ yr	1.5*	– –	–
					Natural Surgical	
Buring (1987)[31]	221	Survey rates	Ever	1.1	1.1 1.0	1.1
			<5 yr	1.0	1.1 1.0	0.9
			5+ yr	1.3	1.3 1.4	1.3
					Natural Surgical	
Wingo (1987)[32]	1369	1645	Ever	1.0	0.8 1.1	1.3
			10–14 yr	0.8	0.7 0.6	1.5
			20+ yr	1.3	– 2.0	1.7
					2 ovaries 1 ovary	
Hunt (1987)[16]	50	Cancer registry rates	Ever	1.6*	1.2 3.1*	1.7
Bergkvist (1989)[33]	253	Regional rates	*Oestrogen in any form*			
			Ever	1.1	–	–
			3–6 yr	1.3	–	–
			9+ yr	1.7*	–	–
			Oestrogen only			
			<0.5 yr	0.8	–	–
			6+ yr	1.8*	–	–
			Combination			
			<0.5 yr	0.5	–	–
			9+ yr	4.4	–	–
			Conjugated oestrogen			
			Ever	1.1	–	–
			<0.5 yr	1.5	–	–
			6+ yr	1.3	–	–
Colditz (1990)[34]	353	Survey rates	Current	1.4*	–	–
			Former	0.9	–	–

* $P<0.05$. [a] Relates to unopposed oestrogens unless otherwise specified.

Table 2. Studies of hormone replacement therapy and endometrial cancer published since 1975.

First author (date of publication)	No. of cases	Relative risk (where 'no use' = 1.0)[a]	Associated risk with: Increased duration	Associated risk with: Increased dose
Smith (1975)[36]	317	7.5*	?	?
Ziel (1975)[37]	94	7.6*	✓	?
Mack (1976)[38]	63	8.0*	✓	✓
McDonald (1977)[39]	145	2.0*	✓	✓
Gray (1977)[40]	205	3.1*	✓	✓
Wigle (1978)[41]	202	2.2*	✓	?
Horwitz (1978)[42]	268[b]	12.0*	?	?
		1.7		
Antunes (1979)[43]	451[b]	6.0*	✓	✓
		2.1		
Jick (1979)[44]	67	11.2*	?	?
Weiss (1979)[45]	322[c]	5.3*	✓	✓
Salmi (1980)[46]	318	0.8	?	?
Jelovsek (1980)[47]	431	2.4*	✓	x
Hulka (1980)[48]	256	3.6*	✓	x
Shapiro (1980)[49]	149	3.9*	✓	?
Stavraky (1981)[50]	206[b]	1.5	✓	✓
		4.8*		
Spengler (1981)[51]	88	2.9*	✓	✓
Obrink (1981)[52]	622	3.7*	✓	?
La Vecchia (1982)[53]	179	2.3*	?	?
Shapiro (1985)[54]	425	3.5*	✓	?
Buring (1986)[55]	188	2.4*	✓	✓

Adapted from Hunt and Vessey as published in the *British Journal of Hospital Medicine*, November 1987. *$P<0.05$. [a] Relates to unopposed oestrogens. [b] Two control groups used. [c] 1–2 years' use.

combined therapy,[16] but this should be interpreted in the light of the authors' analysis which showed that only one of these women had received doses of combined therapy which would now be considered as sufficiently protective to the endometrium.

A consensus report on progestogen use[15] concluded that progestogens were indicated for opposing the effects of oestrogen on the endometrium, but should be used only for those with an intact uterus owing to the possibility of its effects on the cardiovascular system and breast cancer. The survey of general practitioners in Yorkshire, however, showed that 20% of doctors who recognized the association between endometrial cancer and unopposed oestrogen still used this preparation for women who had not had a hysterectomy.[9] This probably relates to insufficient knowledge of the role of progestogen or possibly the recognition of the relationship between progestogen and cardiovascular disease.

Cardiovascular disease

Table 3 illustrates the results of studies relating unopposed and combined therapy to various indicators of cardiovascular disease. It is apparent that the majority of statistically significant results indicate a protective effect for oestrogen, whether the endpoint is fatal or non-fatal disease. However, interpretation is again complicated and methodological reasons have been offered for the contradictory results of the two largest research studies in this area.[75,76] The major problem relates to patient selection — women at high risk of heart disease, for example, those with angina or hypertension, are unlikely to be prescribed hormone replacement therapy, while those who do receive hormone replacement therapy will be at low risk, thus results will underestimate any potential detrimental effects. However, the majority of studies

Table 3. Studies of hormone replacement therapy and cardiovascular disease

First author (date of publication)	Study design	No. of cases	Relative risk (where 'no use' = 1.0)[a]	End points
Burch (1974)[62]	Cohort	9	0.4*	Fatal CHD
Rosenberg (1976)[63]	Case control	336	1.0 (current use)	Non-fatal MI
Pfeffer (1976)[64]	Case control	210	1.1	Non-fatal stroke
Pfeffer (1978)[65]	Case control	185	0.9	MI
Jick (1978)[66]	Case control	17	7.5* (current use)	Non-fatal MI
Gordon (1978)[67]	Cohort	36	1.6	CHD
Hammond (1979)[68]	Cohort	58	0.3*	CAD
Petitti (1979)[69]	Cohort	26	1.2 (current use)	MI
Rosenberg (1980)[70]	Case control	477	1.0 (current use)	Non-fatal MI
Ross (1981)[71]	Case control	133	0.4*	Fatal IHD
Adam (1981)[72]	Case control	76	0.7	Fatal MI
Bain (1981)[73]	Case control	123	0.7 (current use)	Non-fatal MI
			0.9 (use ever)	
Szklo (1984)[74]	Case control	39	0.6	Non-fatal MI
Stampfer (1985)[75]	Cohort	90	0.6 (use ever)	Fatal CHD
			0.3 (current use)	
			0.5* (use ever)	Non-fatal MI
			0.3* (current use)	
			0.5* (use ever)	Total CHD
			0.3* (current use)	
Wilson (1985)[76]	Cohort	116	1.9*	CHD
		51	1.9	MI
		194	1.8*	Total CVD
		48	1.9	Fatal CVD
		45	2.3	Stroke
Henderson (1986)[17]	Cohort	84	0.5*	Fatal MI
Petitti (1986)[77]	Cohort	37	0.5	Fatal CVD
Bush (1987)[78]	Cohort	50	0.4*	Fatal CVD
Hunt (1987)[16]	Cohort	20	0.5*	Fatal IHD
		14	0.7	Fatal stroke and CVD
Paganini-Hill (1988)[79]	Cohort	63	0.5*	Fatal stroke
Thompson (1989)[80]	Case control	603	1.4*	MI and stroke
Avila (1990)[81]	Cohort	120	0.7	Non-fatal MI

*$P<0.05$. [a] Relates to unopposed oestrogens unless otherwise specified. CHD = coronary heart disease. MI = myocardial infarction. CAD = coronary artery disease. IHD = ischaemic heart disease. CVD = cardiovascular disease.

reported adjust for known risks and the protective effect of oestrogen seems to exist.[79,82]

One notable exception is the British study by Thompson and colleagues[80] which found a statistically significant elevated risk in hormone replacement therapy users. However, there are confounding methodological issues, in particular, the hormone replacement therapy users included some progestogen-only users and after excluding these from the analysis, the relative risk remained only slightly elevated and not statistically significant.

Others have argued that additional risk factors such as type of menopause and age at menopause should also be considered,[14] while it has been noted that unknown risk factors and differences in patient groups may be influencing results.[77] The influence of uterine and ovarian status has also been considered in depth in the literature.[83]

One important issue relates to the effect of adding progestogen to oestrogen, as progestogen in users of oral contraceptives has been seen to produce an elevated risk of vascular disease[17] owing to its effect on blood lipoproteins. Although the debate regarding the influence of the route of administration still continues, the weight of available evidence seems to suggest a favourable effect at least for oestrogen and a potentially weaker favourable effect from combined preparations[84,85] although this is still questioned by some.[86]

Discussion

Previous studies have indicated that both women themselves and some general practitioners are unclear about the relative health risks and benefits from oestrogen and progestogen.[9,87] In view of the large volume of sometimes conflicting data, this is perhaps not surprising. There are indications that demand from women for hormone replacement therapy may be rising[88] and general practitioners will need to ensure that the type of hormone replacement therapy prescribed, and the dose and duration of use are appropriate: there is no unequivocal evidence that all women are suitable for hormone replacement therapy. However, the problems associated with decision making in the context of such uncertainty can be lessened if general practitioners are aware of the evidence available, and of the relevant issues in interpreting the evidence. This review provides a summary of some of these issues and evidence and should help to add to the information base available to general practitioners.

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Address for correspondence

Maria K Goddard, Centre for Health Economics, University of York, York YO1 5DD.