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Emergency contraception. Emergency contraception (postcoital contraception) can be used after unprotected intercourse but before a fertilised ovum has been implanted. Methods that act after implantation are considered abortifacients. The two most commonly used emergency contraceptives are *oral contraceptives* and *copper IUDs*.

Oral contraceptive regimens (the so-called 'morning after pill') have historically used a preparation containing high-dose oestrogen with a progestogen, taken within 72 hours of intercourse, and repeated 12 hours later (the Yuzpe regimen). This preparation is thought to act by a variety of mechanisms, which may depend on when in the menstrual cycle it is used. It may prevent implantation, prevent or delay ovulation, disrupt ovum transport, and alter corpus luteum function. However, levonorgestrel alone (without an oestrogen) is now widely recommended as an emergency contraceptive. A large WHO multicentre study found that levonorgestrel 750 micrograms alone within 72 hours of intercourse and repeated after 12 hours was more effective than the Yuzpe regimen and better tolerated.[1] Both regimens were most effective when given within 24 hours of intercourse.[1,2] A small observational study[3] of the Yuzpe method used between 72 and 120 hours after unprotected intercourse reported a trend towards decrease in effectiveness. A further large study[4] by WHO found that for up to 120 hours after intercourse, a single dose of levonorgestrel 1.5 mg was as effective as two doses of 750 micrograms given 12 hours apart, with a pregnancy rate of about 1.5%.

Efficacy rates vary between studies, but the Yuzpe method has been shown to reduce the risk of pregnancy by about 75% and levonorgestrel by about 89%.[5] Based on its greater efficacy and better tolerability, levonorgestrel is now generally recommended as the hormonal emergency contraceptive of choice that can be offered up to 120 hours after intercourse.[5-9]

Copper, but not progestogen, IUDs can be inserted up to 120 hours after unprotected intercourse for postcoital contraception. They have a failure rate of no more than 1% when used for emergency contraception.[9] Thus, when efficacy is a priority the IUD is the emergency contraceptive method of choice.

Mifepristone is under investigation as an emergency contraceptive. Its action appears to depend on inhibiting ovulation or, if ovulation has occurred, preventing implantation. Early studies used a single dose of 600 mg, but later studies have found 10 mg to be equally effective. Mifepristone also appears to be at least as effective as levonorgestrel but it can delay the onset of subsequent menstruation, which might cause anxiety in some women.[10,11]

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Malignant neoplasms. The prophylactic use of oral contraceptives may protect against ovarian cancer in women with mutations of the BRCA1 or BRCA2 genes, but must be balanced against the risk of breast cancer in these women (see Ovary, under Carcinogenicity, p.2061).

Hormone Replacement Therapy

Hormonersatztherapie; HRT; THS; Traitement Hormonal Substitutif; Tratamiento hormonal restitutivo.

Гормонозаместительная Терапия

The Menopause

The menopause is defined as the permanent cessation of cyclical menstruation due to loss of ovarian follicular activity. It is therefore determined in retrospect, conventionally after 1 year without menstruation. In the few years before the menopause (the menopausal transition), ovarian oestradiol secretion declines, sometimes in a fluctuating manner, and there is a resultant increase in pituitary follicle-stimulating hormone (FSH) secretion. The menopausal transition may be characterised by irregular menstrual cycles and dysfunctional uterine bleeding, and fertility is much reduced compared with the early reproductive years. The term perimenopause is used to cover the menopausal transition and the first year after the menopause, and may last 6 years or more. It has sometimes been referred to as the climacteric. Oestrogen concentrations reach their minimum and FSH concentrations their maximum about 4 years after the menopause. After the menopause the ovaries may continue to produce some androgens; adrenal and ovarian androgens are aromatised to oestrogens (predominantly oestrone) in the periphery, but oestrogen concentrations are much lower than in premenopausal women. The median age for the natural menopause is about 51 years. If the menopause occurs in women aged 40 years or less, it is considered premature. The menopause may be induced by surgical removal of both ovaries, or sometimes by antineoplastic drugs or radiotherapy.

The decline in oestrogen concentrations during the perimenopause may be associated with both acute and long-term effects. However, some of these may be difficult to differentiate from the effects of ageing, and the incidence varies geographically. Established *acute symptoms* can include vasomotor instability, manifesting as hot flushes and night sweats, and vaginal atrophy and dyspareunia. Non-specific symptoms include palpitations, headache, backache, and psychological symptoms such as tiredness, lack of concentration, loss of libido, irritability, insomnia, and depression. Insomnia may occur secondary to night sweats. There is little evidence that depressive illness is disproportionately increased at the menopause. Urinary problems are common in ageing women, and may occur in the perimenopause, but the extent that these are due to lack of oestrogens has not been determined. An established *long-term consequence* of the decline in oestrogen concentrations is an increased risk of bone fractures resulting from an increase in the rate of bone resorption. In addition, decline in oestrogen concentrations is associated with adverse effects on blood lipoproteins, and this may be a risk factor for cardiovascular disease.

Acute and longer-term effects of the menopause may be managed by using hormone replacement therapy (HRT) with oestrogens, with or without progestogens, and nonhormonal therapies (see Menopausal Disorders, p.2077).

Adverse Effects of HRT

When oestrogens are used for menopausal HRT, adverse effects include nausea and vomiting, abdominal cramps and bloating, weight changes, breast enlargement and tenderness, premenstrual-like syndrome, sodium and fluid retention, altered blood lipids, cholestatic jaundice, glucose intolerance, rashes and chloasma (melasma), changes in libido, migraine, dizziness, depression, mood changes, headache, leg cramps, vaginal candidiasis, and decreased tolerance of contact lenses. Transdermal delivery systems may cause contact sensitisation (possibly severe hypersensitivity reactions on continued exposure), and nasal sprays may cause local irritation, rhinorrhoea, and epistaxis. Headache has been reported on vigorous exercise. Use of oestrogen without a progestogen results in endometrial hyperplasia and an increased risk of endometrial carcinoma (see below). The addition of a progestogen for 10 to 14 days of a 28-day cycle reduces this risk but results in regular withdrawal bleeding towards the end of the progestogen. Use of continuous progestogen and oestrogen avoids withdrawal bleeding, but may result in irregular breakthrough bleeding, particularly in the early stages of therapy, or if used within 12 months of the last menstrual period. Current use of menopausal HRT is associated with an increased risk of venous thromboembolism and breast cancer (see below).

◊ Reviews.

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Carcinogenicity. Use of unopposed oestrogen as menopausal HRT in women with a uterus increases the risk of endometrial cancer, irrespective of the route of administration. This risk is reduced, although possibly not eliminated completely, by the concomitant use of a progestogen. There is also evidence that use of HRT, as oestrogen alone or with a progestogen, increases the risk of breast cancer.

Because of continuing modifications in regimens for HRT there is a continuing need to monitor the incidence of various cancers in users of this therapy.

The carcinogenicity of combined menopausal HRT has been reviewed.[1]

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BREAST. Early age at menarche and late age at menopause increase the risk of breast cancer, and surgical oophorectomy at an early age decreases the risk of breast cancer. In addition, higher concentrations of unbound endogenous oestrogens in postmenopausal women appear to increase the risk of developing breast cancer.[1] Such risk factors have prompted concerns that menopausal HRT might be associated with an increased risk of breast cancer.

Reviews and analyses[2-4] of studies published during the 1970s and/or 1980s on the use of **unopposed oestrogen** replacement therapy in postmenopausal women have generally shown that there is an associated moderate increase in the risk of breast cancer; figures for overall relative risk compared with non-oestrogen users ranged from under 1 to up to 2. One of these,[3] a meta-analysis of studies from 1976 to 1989, further showed that although the relative risk of breast cancer rose to 1.3 after 15 years of oestrogen use, it did not appear to rise at all until after 5 years of use. A similar meta-analysis[4] differentiated between low-dose oestrogens and high-dose oestrogens; those taking 625 micrograms daily of conjugated oestrogens had a risk of breast cancer 1.08 times higher than non-oestrogen users, whereas the relative risk in those taking 1.25 mg daily or more was up to 2.0. A subsequent meta-analysis[5] differentiated between current use of HRT, duration of use, and use at any time. The highest relative risk of breast cancer was associated with current use (1.4); use for 10 years or more was associated with a relative risk of about 1.2, and having ever used HRT was not associated with an increased risk. In 1997 the Collaborative Group on Hormonal Factors in Breast Cancer reanalysed about 90% of the worldwide evidence on breast cancer and the use of HRT.[6] They reported that the relative risk of having breast cancer diagnosed was increased by a factor of 1.023 for each year of use, being 1.35 for 5 or more years of use. However, this effect was reduced on cessation of use, and had largely disappeared after about 5 years. In women who started therapy at age 50, the cumulative excess number of breast cancers diagnosed per 1000 women between age 50 and 70 were estimated to be 2, 6, and 12 for 5, 10, and 15 years of use, respectively, from a baseline of 45 per 1000 in never-users.[6] In contrast, the arm of the Women's Health Initiative[7] that compared conjugated oestrogens with placebo over an average of about 7 years found a trend towards a reduction in breast cancer risk with HRT. A Finnish cohort study[8] also found no increase in risk with less than 5 years of oral estradiol or estriol therapy. For women taking unopposed oestrogen in the Nurses' Health Study[9] cohort the linear increase in risk with increasing duration of use did not become statistically significant until current use exceeded 20 years.

Most data relate to the use of unopposed oestrogen. There has been speculation both that the concomitant use of progestogen in HRT could reduce the risk of breast cancer and that it might increase it. Bergkvist *et al.*[10] suggested an increased relative risk of

4.4 in the small subgroup using long-term **combined therapy**, but because of the large confidence intervals they considered these results inconclusive. Analysis of the Nurses' Health Study cohort has provided evidence that current use of oestrogen and progestogen is associated with a similar increased relative risk of breast cancer to that of unopposed oestrogen (1.4 versus 1.3).[11] The Collaborative Group on Hormonal Factors in Breast Cancer[6] found no evidence of marked differences between preparations containing oestrogens alone and those containing oestrogens and progestogens. However, in a randomised study, oestrogen plus progestogen was associated with greater increases in radiographic breast density than unopposed oestrogen.[12] The results of further cohort studies[13,14] and case-control studies[15,16] also suggest that the risk of breast cancer may be higher for current or recent use of combined HRT compared with oestrogen alone, and a cohort study[17] of over 1 million women (the Million Women Study) found relative risks of 1.3 for users of oestrogen alone, and 2.0 for combined HRT, compared with never-users. After an average follow-up of about 5 years the Women's Health Initiative,[18] comparing combined HRT with placebo in more than 16 000 women, was stopped early because of an increased rate of invasive breast cancer in women given HRT.

The public health perspective on the **implications** of any increased risk of breast cancer will depend on the background risk. This is high in western countries, so a small increased relative risk would equate to a large absolute increase in number of cases.[19]

If menopausal oestrogen therapy increases the risk of breast cancer, there is a need to ascertain whether these cancers can be detected early, how aggressive they are, and what the mortality rate from them is. Currently, there are limited data on these points.

- There is evidence[20,21] that the use of HRT decreases the sensitivity and specificity of screening mammography (resulting in more false positives and more false negatives), apparently because it increases radiographic breast density[22,23] or slows the natural change from dense patterns to fatty patterns,[24] so decreasing the ability to interpret the mammogram. This is of concern for the success of screening programmes, and has been suggested as a factor in the increased detection of interval cancers (those detected between screening appointments).[25] In addition, HRT-associated increases in radiographic breast density could actually be a marker for risk of breast cancer.[12,26]
- Some data suggest that breast cancers in women on HRT may be of better prognostic grade.[27,28] The Collaborative Group on Hormonal Factors in Breast Cancer reported that breast cancers were more likely to be localised in current or recent users of HRT, but that there was evidence of an increased risk of metastasis with increasing duration of use.[6] However, the Women's Health Initiative[26] did not confirm previous findings of favourable prognosis, and found breast cancers in combined HRT users to be larger, more likely to be node positive, and at a more advanced stage at diagnosis. The likelihood of good prognostic grade in women on HRT may depend on the histological type of any lesion that develops: invasive lobular and tubular cancers are more strongly associated with current use of HRT than invasive ductal cancer.[29]
- Follow-up of most studies is currently insufficient to give a clear indication of mortality risk with long-term use. Early data from a UK cohort study[30] suggested a decreased risk of breast cancer mortality, but after further follow-up the risk was no longer reduced.[31] Similarly, a study in 2614 women with breast cancer followed up for up to 22 years found that the use of HRT at the time of diagnosis was associated with a reduction in mortality, but the effect waned over time.[32] In contrast, data[11] from the Nurses' Health Study cohort suggest an increase in risk of death from breast cancer in women who have currently used HRT for 5 years or more (1.45). Similarly, although mortality was lower overall, a trend towards an increased risk of death from breast cancer (1.9; 95% confidence interval 0.4 to 8.4) was seen in a study of long-term use (mean of 17 years).[33]

The risk of breast cancer may be increased further by the use of HRT in women who are already at an increased risk. Although a study found a modest increase in risk in these women, it was not significantly higher, and there was a reduced total mortality rate.[34] It is unclear whether use of HRT in breast cancer survivors increases the risk of subsequent recurrence and associated mortality (see also Malignant Neoplasms under Precautions, below).

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CERVIX. Studies of the effect of HRT on cervical cancer risk are likely to be subject to the potential confounding of other risk factors such as sexual activity. There are few data on this risk; one study[1] suggested oestrogens do not increase, and may decrease, the risk of cervical cancer, but another[2] suggested that unopposed oestrogen might increase the risk of adenocarcinoma. Therapy with combined HRT did not significantly affect the incidence of cytological abnormalities found in annual cervical smears in women in the Heart and Estrogen/progestin Replacement Study (HERS).[3] In the Women's Health Initiative study,[4] however, there was an overall increase in the incidence of new abnormalities in women given combined HRT, compared with placebo, although the incidence of high-grade squamous intra-epithelial lesion and cervical cancer was not affected.

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ENDOMETRIUM. The increased incidence of endometrial hyperplasia and risk of cancer in women receiving unopposed oestrogen replacement therapy is well established. An analysis of case control studies published during the 1970s and 1980s revealed a relative risk of developing endometrial cancer of 1.4 to 7.6 in women who had ever used oestrogen, and a relative risk of 3.1 to 15 in long-term users, compared with nonusers.[1] Risk was also increased with higher doses of oestrogens. In general, endometrial cancer in oestrogen users was of a better prognostic stage, and survival rates were better, than in nonusers.[1] An elevated risk of endometrial cancer persists for a number of years after stopping unopposed oestrogen therapy.[2]

Addition of a progestogen to oestrogen replacement therapy reduces the incidence of endometrial hyperplasia[3] and cancer. However, the extent to which this alters the risks and benefits of oestrogen replacement therapy, and the optimum progestogen type, and dose and duration, have not been fully elucidated.

As regards risk of endometrial cancer, preliminary data from a cohort study revealed that the addition of cyclical progestogen to oestrogen therapy reduced this risk compared with oestrogen therapy alone.[4] A further case-control study confirmed that progestogens decreased the relative risk, and that the reduction in risk was greater when progestogens were used for 10 or more days per month than when they were used for less than 10 days per month.[5] Two much larger case-control studies have confirmed these findings.[6,7] However, 1 of these studies[6] reported that in long-term users the addition of a progestogen did not reduce the risk of endometrial cancer to that seen in nonusers—after 5 years of use, the relative risk of endometrial cancer with HRT containing 10 or more days of progestogen per month was 2.5 (95% confidence intervals 1.1 to 5.5). This finding remains to be confirmed.

Use of progestogens for 10 days of an 84-day cycle (long cycle) has been suggested to improve acceptability of combined HRT. However, one study of a long-cycle regimen was stopped because of an increased risk of endometrial hyperplasia and atypia compared with a conventional monthly cycle regimen.[8]

Some newer regimens of HRT use continuous low doses of progestogen with oestrogen, which avoid withdrawal bleeding. Data on the incidence of endometrial hyperplasia from randomised trials of these regimens have been reassuring.[3,9,10] Continuous norethisterone plus ethinylestradiol,[9] and continuous medroxyprogesterone plus conjugated oestrogens,[10] protected the endometrium against the hyperplasia seen with the oestrogen alone. Continuous therapy was as effective as cyclical therapy containing 12 days of progestogen,[10] and there is a suggestion from meta-analysis[3] that continuous therapy may even be more effective than sequential when given over a prolonged period, although this remains to be confirmed. The first data on endometrial cancer risk from continuous combined HRT suggest that it is as protective as sequential therapy with the progestogen given for 10 or more days per month (odds ratio 1.07 per 5 years of use for both regimens).[7] The Women's Health Initiative reported[11] that although the rate of endometrial cancer for continuous combined HRT was reduced, it was not significantly different to placebo over 5 years. However, in the analysis of endometrial cancer in the Million Women cohort study,[12] in which 55% of the 716 738 women had not used HRT, there was a lower risk of endometrial cancer with continuous combined HRT, whereas it was not altered for cyclic combined HRT, and was higher for oestrogen-only HRT and tibolone. The beneficial effects of combined HRT were also found to be greatest in obese women.

It is unclear whether use of HRT in endometrial cancer survivors increases the risk of subsequent recurrence and associated mortality (see also Malignant Neoplasms under Precautions, below).

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12. Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2005; **365:** 1543–51.

GASTROINTESTINAL TRACT. Evidence of an effect of oestrogen replacement therapy on colorectal cancer is ambiguous, since studies have reported both an increased and a decreased incidence; a meta-analysis in 1995 suggested no overall effect.[1] However, subsequent cohort studies did suggest a lower incidence of colon cancer in those who had received oestrogens.[2,3] This was most pronounced in current users in whom the relative risk was about one-third to one-half of that for women who had never taken oestrogen. Similarly, a large case-control study also reported a significant reduction in colon cancer, but not rectal cancer.[4] A later meta-analysis[5] concluded that the risk of colon cancer might be decreased among women who have recently used HRT, and that the risk of death from colon cancer might also be reduced. The Women's Health Initiative,[6] a placebo-controlled study of combined HRT in more than 16 000 women, found that those taking HRT had a decreased risk of developing colorectal cancer, but that at diagnosis there was greater lymph node involvement and it was at a more advanced stage.

There is less information on the effect of HRT on death from colorectal cancer. In the Nurses' Health Study cohort[7] there were decreased risks of death from colorectal cancer and death overall for women taking HRT when cancer was diagnosed, compared with those who had never taken HRT. However, this benefit was limited to women who had been taking HRT for no more than 5 years before diagnosis; longer duration of use and past use had no effect on survival.

1. MacLennan SC, *et al.* Colorectal cancer and oestrogen replacement therapy: a meta-analysis of epidemiological studies. *Med J Aust* 1995; **162:** 491–3.
2. Calle EE, *et al.* Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *J Natl Cancer Inst* 1995; **87:** 517–23.
3. Grodstein F, *et al.* Postmenopausal hormone use and risk for colorectal cancer and adenoma. *Ann Intern Med* 1998; **128:** 705–12.
4. Newcomb PA, Storer BE. Postmenopausal hormone use and risk of large-bowel cancer. *J Natl Cancer Inst* 1995; **87:** 1067–71.
5. Nanda K, *et al.* Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol* 1999; **93:** 880–8.
6. Chlebowski RT, *et al.* Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004; **350:** 991–1004.
7. Chan JA, *et al.* Hormone replacement therapy and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006; **24:** 5680–6.

OVARY. There was no clear evidence that the use of oestrogen replacement therapy altered the risk of invasive ovarian cancer in various case-control studies reviewed by the Collaborative Ovarian Cancer Group.[1] However, subsequent study of a large cohort has suggested that long-term oestrogen replacement therapy may increase the risk of fatal ovarian cancer.[2,3] Similarly, a meta-analysis indicated an increased risk for invasive epithelial ovarian cancer, especially after long-term use of HRT.[4] Another, later, cohort study[5] also reported that there was an increased risk of ovarian cancer with oestrogen replacement therapy, particularly when given for 10 years or more, but found no increase for combined HRT. A Swedish case-control study[6] looked at different types of HRT and also found that the risk was increased with oestrogen replacement therapy. For combined HRT, however, the risk was increased for women who had used sequential combined HRT (continuous oestrogen plus cyclical progestogen), but not for those who had used continuous combined HRT. Similarly, in the Women's Health Initiative,[7] a placebo-controlled study of continuous combined HRT in more than 16 000 women, the increased incidence of ovarian cancer was not significant during 5.6 years of follow-up. Further cohort data support an association with long-term current use of unopposed oestrogen replacement therapy,[8-10] but the role of progestogen remains less clear; the Million Women Study[10] also found increased risks with combined HRT, but the Nurses' Health Study[9] found no association. In the cohort NIH-AARP Diet and Health Study[8] the risk of ovarian cancer was also increased overall for 5 or more years of combined HRT use, and found to be higher for users of sequential compared with continuous combined HRT.

1. Whittemore AS, *et al.* Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. *Am J Epidemiol* 1992; **136:** 1184–1203.
2. Rodriguez C, *et al.* Estrogen replacement therapy and fatal ovarian cancer. *Am J Epidemiol* 1995; **141:** 828–35.
3. Rodriguez C, *et al.* Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* 2001; **285:** 1460–5.
4. Garg PP, *et al.* Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. *Obstet Gynecol* 1998; **92:** 472–9.
5. Lacey JV, *et al.* Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 2002; **288:** 334–41. Correction. *ibid.*; 2544.
6. Riman T, *et al.* Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *J Natl Cancer Inst* 2002; **94:** 497–504.
7. Anderson GL, *et al.* Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 2003; **290:** 1739–48.
8. Lacey JV, *et al.* Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. *J Natl Cancer Inst* 2006; **98:** 1397–1405.
9. Danforth KN, *et al.* A prospective study of postmenopausal hormone use and ovarian cancer risk. *Br J Cancer* 2007; **96:** 151–6.
10. Million Women Study Collaborators. Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2007; **369:** 1703–10.

Effects on carbohydrate metabolism. Data from a survey of postmenopausal women showed that diabetic women who were currently taking HRT had better glycaemic control than those who had never taken HRT or were previous users.[1] In the Heart and Estrogen/Progestin Replacement study[2] in postmenopausal women with ischaemic heart disease, there was no significant change in fasting glucose concentrations after 4 years of combined HRT in women with or without diabetes compared with a rise in women given placebo. There was also a lower risk of developing diabetes in those given HRT (cumulative incidence 6.2%) compared with placebo (9.5%). The Women's Health Initiative study[3] reported changes in fasting glucose and insulin concentrations, indicating a fall in insulin resistance, in women treated with combined HRT. During an average 5.6 years of follow-up there was a lower incidence of diabetes in women given HRT (3.5%) compared with placebo (4.2%). This represented an absolute reduction of 15 cases of treated diabetes per 10 000 women per year of HRT treatment.

Although HRT may improve glycaemic control in diabetic postmenopausal women, it is generally used with caution in this group. Diabetic patients are already at increased risk of cardiovascular disease, and HRT may be associated with an increased risk of ischaemic heart disease (see below).

1. Crespo CJ, *et al.* Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care* 2002; **25:** 1675–80.
2. Kanaya AM, *et al.* Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003; **138:** 1–9.
3. Margolis KL, *et al.* Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia* 2004; **47:** 1175–87.

Effects on the cardiovascular system. Various facts support the theory that endogenous oestrogens may be cardioprotective. For example, mortality rates for cardiovascular disease in women are lower than those in men at all ages. In addition, women who have a surgically induced menopause at a young age are at increased risk of ischaemic heart disease compared with women who have a natural menopause.

Conversely, use of high doses of oestrogens for malignant disease is associated with an increased risk of cardiovascular events. Similarly, use of oestrogens in combined oral contraceptives carries a small increased risk of cardiovascular disease (see p.2062). Moreover, an early study in men surviving a myocardial infarction found that high doses of conjugated oestrogens (5 mg daily) were associated with a higher incidence of subsequent coronary events than placebo (see Effects on the Cardiovascular System, in Conjugated Oestrogens, p.2087).

In practice, a number of large observational studies found a decreased risk of ischaemic heart disease and mortality in women receiving menopausal HRT compared with those who have never received this therapy (see below). The reduction in risk was estimated as 30 to 50%, but biases such as the healthy user effect seem to play a part in this estimate; unfortunately, results from controlled studies have cast doubt on the extent of any reduction in risk. There is also evidence to show that HRT *increases* the risk of stroke (see below) and venous thromboembolism (see below).

The mechanisms by which oestrogen exerts its cardiovascular effects are not fully understood.[1] Oestrogen has beneficial effects on lipoproteins, but adverse effects on triglycerides (see below). Similarly, it has beneficial effects on some, and adverse effects on other, mediators of thrombosis. Oestrogen may also have a direct beneficial effect on the coronary vasculature. Progestogens may reduce the beneficial effects of oestrogens on some lipids, although observational data has suggested that this is not sufficient to reverse potential benefit.

1. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999; **340:** 1801–11.

HYPERTENSION. Although high doses of oestrogens have been associated with increased blood pressure, use of menopausal HRT in normotensive and hypertensive women has little effect on blood pressure or may be associated with a small decrease.[1-4] An observational study[5] of normotensive postmenopausal women also found that, over time, the average increase in systolic blood pressure was significantly less in women who were taking HRT.

1. Affinito P, *et al.* Effects of hormonal replacement therapy in postmenopausal hypertensive patients. *Maturitas* 2001; **40:** 75–83.
2. Mueck AO, Seeger H. Effect of hormone therapy on BP in normotensive and hypertensive postmenopausal women. *Maturitas* 2004; **49:** 189–203.
3. Steiner AZ, *et al.* Postmenopausal oral estrogen therapy and blood pressure in normotensive and hypertensive subjects: the Estrogen in the Prevention of Atherosclerosis Trial. *Menopause* 2005; **12:** 728–33.
4. Karalis I, *et al.* Hormone replacement therapy and arterial blood pressure in postmenopausal women with hypertension. *Blood Pressure* 2005; **14:** 38–44.
5. Scuteri A, *et al.* Hormone replacement therapy and longitudinal changes in blood pressure in postmenopausal women. *Ann Intern Med* 2001; **135:** 229–38.

ISCHAEMIC HEART DISEASE. In 1991, Stampfer and Colditz reviewed 31 case-control and cohort studies on the risk of ischaemic heart disease in women using menopausal HRT.[1] Four studies showed an adverse trend, 2 showed no effect on risk, and 25 showed a trend to **reduction in risk** or a significant reduction in risk. The summary relative risk was 0.56, with estimated 95% confidence intervals of 0.50 to 0.61. Other reviews have reported similar reductions in risk.[2,3] Much of the data relate to the use of unopposed oestrogen, which is no longer recommended in women with a uterus because of the risk of endometrial cancer (see above).

There was concern that the **addition of progestogen** might negate or reduce the cardiovascular benefits of oestrogens by reducing the oestrogen-induced rise in serum high-density-lipoprotein cholesterol concentrations. It was postulated that this might be particularly true for progestogens derived from nortestosterone rather than progesterone. Results from the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) indicated that the beneficial effects on blood lipoproteins and fibrinogen, although greatest with unopposed oestrogen, were still present when combined with medroxyprogesterone or micronised progesterone (micronised progesterone was preferable to medroxyprogesterone).[4] Moreover, the UK Medical Research Council Study reported a fairly even balance between possibly beneficial and adverse effects on lipid concentrations and coagulability when conjugated oestrogens alone were compared with conjugated oestrogens plus norgestrel (a nortestosterone derivative).[5] Similar results were reported in the CHART study for ethinylestradiol with or without norethisterone.[6] Although reassuring, these 3 studies provided information only on surrogate endpoints.

Data from the Nurses' Health Study cohort[7] showed a greater reduction in the risk of major ischaemic heart disease among women receiving an oestrogen plus a progestogen (relative risk 0.4) than those receiving an oestrogen alone (0.6), as compared with the risk in women not using hormones. *In-vitro* data suggest that progestogens may actually protect against atherosclerosis via inhibition of smooth muscle cell proliferation.[8]

As regards **duration of HRT use**, current use appeared to be the most important factor for cardiovascular risk reduction. Users with coronary risk factors appeared to derive greater benefit from HRT than those at low risk of coronary artery disease.[9] Of concern, the Nurses' Health Study reported that the apparent benefit from HRT decreased with increasing duration of use beyond 10 years because of an increase in mortality from breast cancer.[9]

However, a number of studies have now found **no beneficial effect** on risk of heart disease. In contrast to previous findings, a retrospective case-control study[10] did not find a decreased risk of myocardial infarction in women currently using combined HRT or oestrogens alone. The authors of this study suggested that the benefit of HRT may not be as large as has been estimated in some qualitative overviews, and emphasised the need for data from randomised studies.[10] This has been confirmed by results[11] of the Heart and Estrogen/Progestin Replacement Study, a randomised placebo-controlled study in women with established ischaemic heart disease. Combined HRT with conjugated oestrogens plus medroxyprogesterone produced no overall reduction in the occurrence of myocardial infarction or death due to ischaemic heart disease in these women. This overall lack of effect was due to an initial increase in cardiac events during the first year, with a later beneficial effect in years 3 to 5. During unblinded follow-up[12] of 2.7 years, these late beneficial effects did not persist and the risk of cardiovascular events was not reduced. Observational data from the Nurses' Health Study cohort[13] also noted a trend towards an initial increase in cardiac events followed by a decrease in risk with long-term use of HRT, in women with a history of ischaemic heart disease. Other studies found that HRT did not affect the progression of existing coronary atherosclerosis as measured by angiography.[14,15] Oestrogen therapy for 2 years also had no effect on the risk of further cardiac events in postmenopausal women who had survived a myocardial infarction.[16] There is also some evidence that the risks and benefits of HRT may vary according to the presence or absence of particular prothrombotic mutations.[17]

These worrying results have suggested that HRT should **not** be used for secondary prevention in women with heart disease, in contrast to some earlier suggestions (see also Cardiovascular Disorders under Uses and Administration, below).

In women without pre-existing heart disease, observational data from the Nurses' Health Study[18] showed a reduced risk of major coronary events in users of HRT, compared with never-users. However, there were increased rates of coronary events at an average follow-up of about 5 years in the Women's Health Initia-

tive,[19] a primary prevention study comparing combined HRT with placebo in over 16 000 women. The risk was highest in the first year of HRT but decreased to a smaller non-significant excess risk in the following years.[20] The arm of the Women's Health Initiative that compared unopposed conjugated oestrogens with placebo in more than 10 000 women with prior hysterectomy found that over an average of 7 years there was no difference in the risk of ischaemic heart disease.[21,22] These results suggest that HRT should also **not** be used for primary prevention of ischaemic heart disease.

There is continuing debate about the effect of HRT on ischaemic heart disease, and how it might be influenced by age. The generalisability of some study results, such as in the Women's Health Initiative, has been questioned because the mean age of the study group has been much older than women who generally take HRT for vasomotor symptoms in their 50s. A meta-analysis[23] has compared data from younger and older women, and found that for younger women (less than 10 years since menopause or under 60 years of age) there was a reduced risk of myocardial infarction or cardiac death with HRT. In older women, however, events increased in the first year then decreased after 2 years, resulting in a neutral effect over time. Secondary analysis[24] of the Women's Health Initiative data found that for women who started HRT closer to menopause (aged 50 to 59 years or less than 10 years since menopause) there was a trend towards reduced risks of ischaemic heart disease and death, while risk increased with age and time since menopause. One factor might be the reduction by HRT of atherosclerotic calcification in the coronary arteries.[25] Further studies are underway to examine the effect of HRT, started soon after menopause, in the prevention of atherosclerosis.

1. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991; **20:** 47–63.
2. Grady D, *et al.* Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992; **117:** 1016–37.
3. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. *JAMA* 1991; **265:** 1861–7.
4. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995; **273:** 199–208. Correction. *ibid.*; **274:** 1676.
5. Medical Research Council's General Practice Research Framework. Randomised comparison of oestrogen versus oestrogen plus progestogen hormone replacement therapy in women with hysterectomy. *BMJ* 1996; **312:** 473–8.
6. Speroff L, *et al.* The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART Study): a randomized controlled trial. *JAMA* 1996; **276:** 1397–1403.
7. Grodstein F, *et al.* Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; **335:** 453–61. Correction. *ibid.*; 1046.
8. Lee W-S, *et al.* Progesterone inhibits arterial smooth muscle cell proliferation. *Nature Med* 1997; **3:** 1005–1008.
9. Grodstein F, *et al.* Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997; **336:** 1769–75.
10. Sidney S, *et al.* Myocardial infarction and the use of estrogen and estrogen-progestogen in postmenopausal women. *Ann Intern Med* 1997; **127:** 501–8.
11. Hulley S, *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998; **280:** 605–13.
12. Grady D, *et al.* Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 49–57. Correction. *ibid.*; 1064.
13. Grodstein F, *et al.* Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study: a prospective, observational study. *Ann Intern Med* 2001; **135:** 1–8.
14. Herrington DM, *et al.* Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000; **343:** 522–9.
15. Hodis HN, *et al.* Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003; **349:** 535–45.
16. The ESPRIT team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002; **360:** 2001–8.
17. Psaty BM, *et al.* Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. *JAMA* 2001; **285:** 906–13.
18. Grodstein F, *et al.* A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; **133:** 933–41.
19. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.
20. Manson JE, *et al.* Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003; **349:** 523–34.
21. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; **291:** 1701–12.
22. Hsia J, *et al.* Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006; **166:** 357–65.
23. Salpeter SR, *et al.* Coronary heart disease events associated with hormone therapy in younger and older women. *J Gen Intern Med* 2006; **21:** 363–6.
24. Rossouw JE, *et al.* Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; **297:** 1465–77. Correction. *ibid.* 2008; **299:** 1426.
25. Manson JE, *et al.* WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007; **356:** 2591–2602.

STROKE. The Framingham Study suggested a more than two-fold increased risk of stroke in women using menopausal HRT.[1] However, subsequent studies reporting risk of stroke separately from other cardiovascular events showed either no effect on risk[2] or a decreased risk in the order of 30 to 50%.[3,4]

Data from the Nurses' Health Study cohort[5] revealed little association between the risk of stroke of any type and current use of unopposed oestrogens or oestrogen plus progestogen. However, they reported a trend towards an increased risk of stroke in current users of high-dose oestrogen therapy (1.25 mg or higher). Similarly, a large Danish case-control study found that unopposed oestrogens or oestrogen plus progestogen had no effect on the risk of non-fatal haemorrhagic or thromboembolic stroke,[6] and data from the Heart and Estrogen/Progestin Replacement Study indicated that combined HRT in women with pre-existing ischaemic heart disease had no effect on risk of stroke.[7,8] In contrast to these results, the Women's Health Initiative, a placebo-controlled study of over 16 000 healthy women, found that combined HRT increased the risk of ischaemic stroke, and that the increase in risk became apparent after about 1 year of starting HRT.[9] Furthermore, the arm of the Women's Health Initiative that compared unopposed conjugated oestrogens with placebo in more than 10 000 women with prior hysterectomy also found an increased risk of stroke;[10] additional data and analysis also confirmed that the increased risk was for ischaemic stroke, and appeared after about 4 years.[11] Although the numbers of haemorrhagic strokes were small in both Women's Health Initiative studies, the combined data showed no significant effect of hormone therapy.[11] A systematic review,[12] which was dominated by the results of the Women's Health Initiative, found that HRT was associated with an increase in stroke. This was attributed largely to ischaemic stroke, whereas there was no significant change in the risks of haemorrhagic stroke, fatal stroke, or transient ischaemic attack. A poor outcome (death or dependency) was also found to be more likely with HRT. Secondary analysis[13] of the Women's Health Initiative data also found that the risk of stroke was increased regardless of years since menopause.

In a controlled study in postmenopausal women who had recently had a stroke or transient ischaemic attack, the use of unopposed oestrogen had no significant effect on mortality or the recurrence of stroke.[14]

1. Wilson PWF, *et al.* Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: the Framingham study. *N Engl J Med* 1985; **313:** 1038–43.
2. Stampfer MJ, *et al.* Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *N Engl J Med* 1991; **325:** 756–62.
3. Paganini-Hill A, *et al.* Postmenopausal oestrogen treatment and stroke: a prospective study. *BMJ* 1988; **297:** 519–22.
4. Finucane FF, *et al.* Decreased risk of stroke among postmenopausal hormone users: results from a national cohort. *Arch Intern Med* 1993; **153:** 73–9.
5. Grodstein F, *et al.* Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; **335:** 453–61. Correction. *ibid.*; 1406.
6. Tønnes Pedersen A, *et al.* Hormone replacement therapy and risk of non-fatal stroke. *Lancet* 1997; **350:** 1277–83.
7. Simon JA, *et al.* Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* 2001; **103:** 638–42.
8. Grady D, *et al.* Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 49–57. Correction. *ibid.*; 1064.
9. Wassertheil-Smoller S, *et al.* Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003; **289:** 2673–84.
10. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; **291:** 1701–12.
11. Hendrix SL, *et al.* Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* 2006; **113:** 2425–34.
12. Bath PMW, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 2005; **330:** 342–4.
13. Rossouw JE, *et al.* Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; **297:** 1465–77. Correction. *ibid.* 2008; **299:** 1426.
14. Viscoli CM, *et al.* A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001; **345:** 1243–9.

VENOUS THROMBOEMBOLISM. Traditionally it has been assumed that, unlike combined oral contraceptives, menopausal HRT is not associated with an increased risk of venous thromboembolism.

However, observational studies have provided substantial evidence that there is an increased risk of deep-vein thrombosis and/or pulmonary embolism in women receiving HRT.[1-4] The relative risk of venous thromboembolism was found to be 2.1 to 3.6 in current users compared with past-users or those who had never received HRT. This equates to an excess of 16 to 23 cases per 100 000 women per year. One study found that the increase in risk was restricted to the first year of use.[4] Another reported an increased risk with increasing oestrogen dose.[2]

Evidence from later randomised placebo-controlled studies[5-8] supports the findings of the observational studies above. Results from the Women's Health Initiative also suggest that the risk is higher with combined HRT than oestrogen alone.[9] It has been suggested that transdermal HRT might be preferable in women with a history of thromboembolism (see Administration, below) and a case-control study[10] reported that unlike oral preparations, transdermal oestrogen was not associated with an increased risk of venous thromboembolism.

The UK CSM considers that the absolute risk of venous thromboembolism in all women using HRT is higher than was originally suggested, and that the risks are higher particularly in older women and in women with predisposing factors, such as a history of venous thromboembolism.[11] Women with the factor V Leiden thrombophilia are at high risk of developing venous thromboembolism when taking HRT. The pooled results of 2 studies showed[12] that in the presence of this thrombophilia alone the odds ratio of developing venous thromboembolism was 3.58, and for HRT alone was 3.16, but women who had both these risk factors had a much higher risk of 13.16.

1. Daly E, *et al.* Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996; **348:** 977–80.
2. Jick H, *et al.* Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 1996; **348:** 981–83.
3. Grodstein F, *et al.* Prospective study of exogenous hormones and risk of pulmonary embolism in women. *Lancet* 1996; **348:** 983–7.
4. Pérez Gutthann S, *et al.* Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ* 1997; **314:** 796–800.
5. Grady D, *et al.* Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2000; **132:** 689–96. Correction. *ibid.* 2001; **134:** 81.
6. Hulley S, *et al.* Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 58–66.
7. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.
8. Cushman M, *et al.* Women's Health Initiative Investigation. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004; **292:** 1573–80.
9. Curb JD, *et al.* Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006; **166:** 772–80.
10. Canonico M, *et al.* Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007; **115:** 840–5.
11. CSM/MCA. New product information for hormone replacement therapy. *Current Problems* 2002; **28:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 23/01/08)
12. Wu O, *et al.* Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thromb Haemost* 2005; **94:** 17–25.

Effects on the eyes. The risk of dry eye increases with age, when tear production normally decreases. The incidence is higher in women, but it is unclear whether sex hormone changes in perimenopausal and postmenopausal women play a role in ocular surface dysfunction.[1] The effects of HRT on the incidence and management of dry eye have been debated. Relief of symptoms has occurred in some women given HRT[1] and improvements in tests of tear function and conjunctival epithelium have been reported.[2] However, a large cohort study[3] found a higher prevalence of dry eye syndrome in women taking HRT, particularly oestrogen alone, than in those not taking HRT.

1. Versura P, Campos EC. Menopause and dry eye: a possible relationship. *Gynecol Endocrinol* 2005; **20:** 289–98.
2. Pelit A, *et al.* Tear function tests and conjunctival impression cytology before and after hormone replacement therapy in postmenopausal women. *Eur J Ophthalmol* 2003; **13:** 337–42.
3. Schaumberg DA, *et al.* Hormone replacement therapy and dry eye syndrome. *JAMA* 2001; **286:** 2114–19.

Effects on the gallbladder. The use of HRT is reported to increase the risk of gallstone formation and cholecystectomy in postmenopausal women.[1-4]

1. Uhler ML, *et al.* Estrogen replacement therapy and gallbladder disease in postmenopausal women. *Menopause* 2000; **7:** 162–7.
2. Simon JA, *et al.* Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2001; **135:** 493–501.
3. Hulley S, *et al.* Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 58–66.
4. Cirillo DJ, *et al.* Effect of estrogen therapy on gallbladder disease. *JAMA* 2005; **293:** 330–9.

Effects on lipids. Oestrogens increase serum high-density-lipoprotein cholesterol and decrease low-density-lipoprotein cholesterol concentrations, effects that are considered favourable and may be a mechanism behind their apparent reduction in ischaemic heart disease in postmenopausal women, although controlled studies have not found combined HRT to reduce coronary events (see Effects on the Cardiovascular System, above). Oestrogens may also increase serum triglyceride concentrations, which is undesirable. Severe hypertriglyceridaemia and pancre-

atitis have occurred in women with hypertriglyceridaemia treated with oestrogens.[1,2] Use of concomitant progestogen reduces oestrogen-induced hypertriglyceridaemia.[2]

1. Glueck CJ, *et al.* Severe hypertriglyceridemia and pancreatitis when estrogen replacement therapy is given to hypertriglyceridemic women. *J Lab Clin Med* 1994; **123:** 59–64.
2. Isley WL, Oki J. Estrogen-induced pancreatitis after discontinuation of concomitant medroxyprogesterone therapy. *Am J Med* 1997; **102:** 416–17.

Effects on mental function. For results suggesting that HRT may increase the risk of developing dementia see under Uses and Administration, below.

Effects on the pancreas. Unopposed oestrogen has been associated with pancreatitis in women with hypertriglyceridaemia (see Effects on Lipids, above). There have also been a few cases of pancreatitis, attributed to HRT, in which triglyceride concentrations were within the normal range.[1,2]

1. Blake WED, Pitcher ME. Estrogen-related pancreatitis in the setting of normal plasma lipids: case report. *Menopause* 2003; **10:** 99–101.
2. Trenque-Tessereau M-GB, *et al.* Combined estradiol/gestodene and acute pancreatitis. *Ann Pharmacother* 2005; **39:** 1953–4.

Precautions

Before menopausal HRT is given the woman should undergo an appropriate medical examination and her medical history should be carefully evaluated. Regular examination is recommended during use.

HRT should be avoided in women with active thrombophlebitis or thromboembolic disease; it should not be given to those with a history of recurrent thromboembolism unless they are already receiving anticoagulant treatment.

HRT should not be given to those with undiagnosed abnormal vaginal bleeding, and abnormal vaginal bleeding during therapy should be investigated (see below). HRT is also contra-indicated in women with oestrogen-dependent neoplasms such as those of the breast or endometrium, and is usually considered contra-indicated in women with a history of these conditions although this has been debated (see below). Active liver disease and Dubin-Johnson or Rotor syndromes are also generally considered to be contra-indications.

Prolonged exposure to unopposed oestrogens increases the risk of endometrial cancer whatever the route of administration (see above). HRT should be used with caution in women with antiphospholipid antibodies or predisposing factors to thromboembolism (see also Venous Thromboembolism, above), and in migraine, a history of breast nodules or fibrocystic disease, uterine fibroids, or a history of endometriosis. HRT should also be used with caution in women with diabetes because of the increased risk of heart disease. Consideration should be given to temporarily stopping HRT 4 to 6 weeks before elective surgery (but see also below).

HRT should be stopped immediately, and appropriate investigations and treatment carried out, if any of the following occur:

- sudden severe chest pain, sudden breathlessness, or severe pain/swelling in calf of one leg (possibly indicative of thromboembolic complications)
- unusual, severe, prolonged headache, sudden disturbances of vision or hearing or other perceptual disorders, collapse, marked numbness or weakness affecting one side of the body, or other signs or symptoms suggestive of cerebrovascular accident
- a first unexplained epileptic seizure
- hepatitis, jaundice, generalised itching, liver enlargement, severe upper abdominal pain
- significant rise in blood pressure (above 160 mmHg systolic or 100 mmHg diastolic)
- clear exacerbation of other conditions known to be capable of deteriorating during HRT or pregnancy.

Although evidence is in many cases less well established, HRT should perhaps also be used with caution in diseases which may be exacerbated during pregnancy or oestrogen therapy including asthma, epilepsy, hypertension, renal disease, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and SLE.

Doses of oestrogen in HRT are insufficient to provide contraception. HRT is contra-indicated in known or suspected pregnancy, and in women who are breast feeding.

Endometriosis. Women with endometriosis who are treated with hysterectomy and bilateral oophorectomy undergo a surgically-induced menopause and can experience acute menopausal symptoms; they are also at risk of conditions such as osteoporosis from long-term oestrogen deficiency. HRT until about 50 years of age has been recommended for women who undergo premature menopause, but disease reactivation and malignant transformation to adenocarcinoma in residual foci have been reported in women with a history of endometriosis, particularly with unopposed oestrogen. Although there are limited data to quantify the risks from HRT, they appear to be small. Nevertheless, recurrent disease may be more severe, with a greater chance of causing ureteric obstruction and consequent renal damage. To minimise the risks of reactivation and malignancy, women with a history of endometriosis should probably be given continuous combined HRT at the lowest effective dose. Although witholding HRT for a few months to wait for endometriosis to regress after surgery has been recommended, there is limited supporting evidence and others suggest that HRT may be started soon after surgery.[1]

1. Soliman NF, Hillard TC. Hormone replacement therapy in women with past history of endometriosis. *Climacteric* 2006; **9:** 325–35.

Lupus erythematosus. SLE is an auto-immune disease which is far more common in women than in men, and usually has a peak onset for women in their 20s and 30s. There is some evidence to suggest that menopausal HRT use may be associated with a slightly increased risk in the onset of SLE in older women.[1-3] In women with pre-existing SLE, small studies found no apparent effect of HRT on disease flares.[2] In a larger study of 351 women, who were given either combined HRT or placebo for 12 months, severe flares were rare in both groups but mild to moderate flares were increased in the HRT group.[4]

Women with SLE are at increased risk of thromboembolic disease, and it has been suggested that transdermal oestrogen HRT may have less of a thrombogenic effect than oral HRT.[5] Women with antiphospholipid antibodies (which includes about a third of all patients with SLE) are at the highest risk and some[5] suggest that HRT should be avoided altogether in patients with persistent antibodies.

1. Petri M. Exogenous estrogen in systemic lupus erythematosus: oral contraceptives and hormone replacement therapy. *Lupus* 2001; **10:** 222–6.
2. Mok CC, *et al.* Use of exogenous estrogens in systemic lupus erythematosus. *Semin Arthritis Rheum* 2001; **30:** 426–35.
3. Costenbader KH, *et al.* Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007; **56:** 1251–62.
4. Buyon JP, *et al.* The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. *Ann Intern Med* 2005; **142:** 953–62.
5. Gompel A, Piette JC. Systemic lupus erythematosus and hormone replacement therapy. *Menopause Int* 2007; **13:** 65–70.

Malignant neoplasms. HRT is usually avoided in women who have been treated for *breast cancer* because of the concern that oestrogen will stimulate cancer recurrence. A retrospective observational study[1] and a retrospective case-control study[2] among women diagnosed with breast cancer did not find any evidence of an adverse effect in those who began HRT after diagnosis. A systematic review[3] of studies of HRT in breast cancer survivors reached a similar conclusion, but also noted that these studies were small, not randomised, and many were uncontrolled. More recently, an open randomised study[4] was stopped early when it was found that 2 years of HRT increased the risk of breast cancer (local recurrence, contralateral cancer, or distant metastases); this has cast doubt on the safety of HRT in these patients. A similar study, however, found that about 4 years of HRT did not increase the risk of cancer recurrence.[5] Comparing these two results, the authors suggested that the increased risk may have been due to the use of combined HRT that included continuous progestogen, rather than cyclic or long-cycle regimens. A systematic review[6] of 20 studies, including these two, highlighted the many differences in design such as HRT regimens used, and concluded that in the absence of sufficient evidence of safety HRT should not be used in women with a history of breast cancer. Other reviewers[7] have also recommended a cautious approach, suggesting that HRT should not be used for first-line management of menopausal symptoms in these women, but may be justified when other treatments have failed. The safety of different HRT regimens requires further study,[6,7] and the use of tibolone is under investigation.[8]

Similarly, HRT is usually avoided in patients who have been treated for *endometrial cancer*, because of the theoretical risk of stimulating tumour recurrence.[9] There is a lack of well-designed studies on this subject, but some data suggest that HRT might not increase the rate of recurrence or death.[10,11]

Women who carry *mutations of the BRCA1 and BRCA2 genes* are at greatly increased risk of breast and ovarian cancers, and prophylactic oophorectomy after child-bearing may be considered as a means of reducing this risk. The use of HRT to manage the subsequent menopausal symptoms has been controversial because of concerns that it may adversely affect the risk of breast cancer. One study[12] that used a decision analytical model concluded that HRT did not negate the benefits of oophorectomy; the degree of life expectancy loss or gain was relatively small and influenced by length of HRT use, age at oophorectomy, and presence or absence of concurrent mastectomy. The authors suggested that the decision to use short-term HRT should be based on quality of life issues rather than life expectancy, and that HRT should be stopped at or before the expected age of natural menopause. A subsequent cohort study[13] also found that the use of HRT did not negate the protective effect of prophylactic oophorectomy against breast cancer in BRCA1/2 mutation carriers. Despite these reassuring results, data are limited and further studies are needed to determine appropriate formulations and the optimal timing and duration of HRT for these women.[14]

1. Durna EM, *et al.* Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. *Med J Aust* 2002; **177:** 347–51.
2. O'Meara ES, *et al.* Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst* 2001; **93:** 754–62.
3. Col NF, *et al.* Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol* 2001; **19:** 2357–63.
4. Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. *Lancet* 2004; **363:** 453–5.
5. von Schoultz E, *et al.* Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst* 2005; **97:** 533–5.
6. Antoine C, *et al.* Safety of hormone therapy after breast cancer: a qualitative systematic review. *Hum Reprod* 2007; **22:** 616–22.
7. Hickey M, *et al.* Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. *Lancet Oncol* 2005; **6:** 687–95.
8. Baber R, *et al.* Therapy for menopausal symptoms during and after treatment for breast cancer: safety considerations. *Drug Safety* 2005; **28:** 1085–1100.
9. Committee on Gynecologic Practice. ACOG committee opinion: hormone replacement therapy in women treated for endometrial cancer (number 235, May 2000). *Int J Gynecol Obstet* 2001; **73:** 283–4.
10. Suriano KA, *et al.* Estrogen replacement therapy in endometrial cancer patients: a matched control study. *Obstet Gynecol* 2001; **97:** 555–60.
11. Barakat RR, *et al.* Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2006; **24:** 587–92.
12. Armstrong K, *et al.* Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. *J Clin Oncol* 2004; **22:** 1045–54.
13. Rebbeck TR, *et al.* Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2005; **23:** 7804–10.
14. Rubinstein WS. Surgical management of BRCA1 and BRCA2 carriers: bitter choices slightly sweetened. *J Clin Oncol* 2005; **23:** 7772–4.

Porphyria. HRT should be used with caution in patients with porphyria.

Surgery. A review[1] recommended that women receiving HRT and due to have major elective surgery or leg surgery should continue taking the HRT and should routinely receive thromboprophylaxis (e.g. subcutaneous low-molecular-weight heparins and the use of graduated elastic compression stockings) in the perioperative period. Similar management was proposed when undergoing emergency surgery but prophylaxis was considered unnecessary with minor surgery. These conclusions were based on the advice of specialist groups but it was noted that there was some conflict with recommendations of manufacturers and those of the *BNF*. The *BNF* states that it may be prudent to stop HRT 4 to 6 weeks before major surgery; failing that, prophylaxis as above is recommended. HRT should only be restarted after full mobilisation.

1. Anonymous. Drugs in the peri-operative period: hormonal contraceptives and hormone replacement therapy. *Drug Ther Bull* 1999; **37:** 78–80.

Vaginal bleeding. Menopausal HRT is contra-indicated in patients with undiagnosed abnormal vaginal bleeding, which may be a symptom of endometrial carcinoma. The causes of abnormal vaginal bleeding in women receiving HRT and guidelines on their investigation and treatment have been reviewed.[1-3]

1. Good AE. Diagnostic options for assessment of postmenopausal bleeding. *Mayo Clin Proc* 1997; **72:** 345–9.
2. Spencer CP, *et al.* Management of abnormal bleeding in women receiving hormone replacement therapy. *BMJ* 1997; **315:** 37–42.
3. Oehler MK, *et al.* Assessment of abnormal bleeding in menopausal women: an update. *J Br Menopause Soc* 2003; **9:** 117–21.

Withdrawal. Although it is now generally recommended that menopausal HRT used to relieve vasomotor and vaginal symptoms should be given at the lowest effective dose for no longer than necessary (see Menopausal Disorders, p.2077), there has been little study of how to effectively withdraw HRT without a recurrence of menopausal symptoms. When the Women's Health Initiative (WHI) study was stopped prematurely, the effect of HRT withdrawal was assessed in 8405 of the women in this study who were receiving either combined HRT or placebo at the time.[1] A range of menopausal symptoms were reported in both groups. Moderate to severe vasomotor symptoms (hot flushes and night sweats) occurred in 21.2% of women who

stopped HRT, compared with 4.8% stopping placebo; younger women were more likely to develop symptoms. Pain and stiffness was reported by about 37% who stopped HRT, with a similar incidence across age groups. Having these symptoms at study entry was the strongest factor for recurrence when treatment ended.

Once the WHI study was stopped, many other women were also advised, or independently chose, to stop HRT; retrospective studies in smaller groups have reported the recurrence of troublesome menopausal symptoms in 30% or more.[2-4] There also appeared to be no advantage to tapering the withdrawal of HRT, compared with stopping abruptly.[2,3] Women reported using various measures to manage recurrent menopausal symptoms,[1,3,4] including lifestyle management such as exercise and drinking more fluids, vaginal oestrogen therapy, antidepressants, and preparations such as cimicifuga (black cohosh), soya, or red clover; in some cases women restarted HRT.

1. Ockene JK, *et al.* Symptom experience after discontinuing use of estrogen plus progestin. *JAMA* 2005; **294:** 183–93.
2. Grady D, *et al.* Predictors of difficulty when discontinuing postmenopausal hormone therapy. *Obstet Gynecol* 2003; **102:** 1233–9.
3. Haskell SG. After the Women's Health Initiative: postmenopausal women's experiences with discontinuing estrogen replacement therapy. *J Womens Health (Larchmt)* 2004; **13:** 438–42.
4. Ness J, *et al.* Menopausal symptoms after cessation of hormone replacement therapy. *Maturitas* 2006; **53:** 356–61.

Interactions

Drugs that increase the hepatic metabolism of oestrogens and progestogens have been associated with failure of the combined oral contraceptive (see p.2067). Important examples include rifamycins, some antiepileptics, and griseofulvin. It is not unreasonable to assume that these drugs would also be associated with decreased effectiveness of HRT, but there appears to be little information on this (for one report, see Antiepileptics, below).

Although oral contraceptives alter the effects of a number of drugs (see p.2067), the lower doses of oestrogens used in HRT are considered less likely to induce interactions, although the possibility remains.

◊ A study[1] in 12 healthy women aged 20 to 25 years, using bupropion as a probe reaction, found that HRT (estradiol valerate with levonorgestrel) was an inhibitor of the cytochrome P450 isoenzyme CYP2B6.

1. Palovaara S, *et al.* Inhibition of cytochrome P450 2B6 activity by hormone replacement therapy and oral contraceptive as measured by bupropion hydroxylation. *Clin Pharmacol Ther* 2003; **74:** 326–33.

Alcohol. Acute ingestion of an alcoholic beverage led to a threefold increase in circulating estradiol in a study of women on menopausal HRT.[1] Another study[2] that included 309 women taking HRT found that about half had low serum-oestradiol concentrations, and that moderate alcohol consumption was one of the factors associated with achieving therapeutic concentrations.

Both alcohol consumption and HRT are risk factors for breast cancer, and cohort studies[3,4] have suggested that the risk from the combination may be higher than the individual risks alone.

1. Ginsburg ES, *et al.* Effects of alcohol ingestion on estrogens in postmenopausal women. *JAMA* 1996; **276:** 1747–51.
2. Gavaler JS. Oral hormone replacement therapy: factors that influence the estradiol concentrations achieved in a multiracial study population. *J Clin Pharmacol* 2002; **42:** 137–44.
3. Chen WY, *et al.* Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. *Ann Intern Med* 2002; **137:** 798–804.
4. Zhang SM, *et al.* Alcohol consumption and breast cancer risk in the Women's Health Study. *Am J Epidemiol* 2007; **165:** 667–76.

Antiepileptics. *Phenytoin* was reported to reduce the effect of conjugated oestrogens in a menopausal woman.[1]

1. Notelovitz M, *et al.* Interaction between estrogen and Dilantin in a menopausal woman. *N Engl J Med* 1981; **304:** 788–9.

Levothyroxine. Increased doses of levothyroxine may be needed in hypothyroid women who receive oestrogens for postmenopausal HRT—see p.2173.

Tacrine. HRT may increase plasma concentrations of tacrine—see p.370.

Vitamins. The effect of oral *ascorbic acid* (500 mg twice daily) on plasma concentrations of oestradiol was studied in 25 postmenopausal women stabilised on transdermal estradiol gel.[1] After 1 month, oestradiol concentrations had risen for the group overall by about 21%. The greatest responses were in those who initially had low plasma concentrations of ascorbic acid or oestradiol. The authors suggested that the antoxidant effect of ascorbic acid might reverse the oxidation of oestrogens, but that these results did not support the general use of ascorbic acid as an adjuvant to HRT.

1. Vihtamäki T, *et al.* Oral ascorbic acid increases plasma oestradiol during postmenopausal hormone replacement therapy. *Maturitas* 2002; **42:** 129–35.

Pharmacokinetics

For a discussion of the pharmacokinetics of oestrogens and progestogens, see Estradiol, p.2098 and Progesterone, p.2126, respectively. The extent of binding of progestogens to serum sex-hormone binding globulin may be altered when they are given with an oestrogen. Oestrogens increase serum concentrations of sex-hormone binding globulin, and progestogens differ in their ability to suppress this effect.

Uses and Administration

The term *hormone replacement therapy* (HRT) is often used to represent the use of an oestrogen, with or without a progestogen, in peri- and postmenopausal women. HRT is used for the management of acute menopausal symptoms such as vasomotor symptoms and atrophic vaginitis, and can be used long-term in women with premature or surgically-induced menopause until the normal age of menopause. HRT may also be used for postmenopausal osteoporosis in selected women, when other preferred drugs cannot be used or have been ineffective. The most commonly used oestrogens in menopausal HRT are natural oestrogens such as estradiol, and conjugated oestrogens. Dosages of oestrogens used in HRT are generally lower than those used in combined oral contraceptives, and do not therefore provide contraception.

Oestrogens for HRT are available as oral tablets, intranasal sprays, subcutaneous implants, topical applications for vulvovaginal use, intravaginal rings, and transdermal patches and gels. Generally, if prolonged therapy (for more than 2 to 4 weeks) with an oestrogen by any route is envisaged in a woman with an intact uterus, a progestogen is required to prevent endometrial proliferation. This may be given by mouth cyclically for 10 to 14 days per cycle or continuously; transdermal preparations that supply both oestrogen and progestogen are now also available. Both progesterone derivatives such as medroxyprogesterone and dydrogesterone, and 19-nortestosterone analogues such as norethisterone, norgestrel, and levonorgestrel are used. Doses of progestogens for HRT are similar to those used in combined oral contraceptives.

Administration. In a discussion of the relative merits of oral and transdermal oestrogen therapy[1] it was suggested that there was circumstantial and theoretical evidence to suppose that transdermal therapy might be preferable in women who smoke, who suffer from migraine, hepatobiliary disease, or hypertriglyceridaemia, or who have a history of thromboembolism. In contrast, oral HRT might be preferable in patients with hypercholesterolaemia. However, studies to examine these suppositions were needed. Although there have been further studies comparing cardiovascular risk markers in women given oral or transdermal HRT, data on clinical outcome are scarce[2] (see also Venous Thromboembolism, under Adverse Effects, above). Various alternatives to oral oestrogen therapy have been reviewed.[3-5] For reviews of estradiol given as implants or transdermally, see p.2099.

1. Lufkin EG, Ory SJ. Relative value of transdermal and oral estrogen therapy in various clinical situations. *Mayo Clin Proc* 1994; **69:** 131–5.
2. Modena MG, *et al.* New evidence regarding hormone replacement therapies is urgently required: transdermal postmenopausal hormone therapy differs from oral hormone therapy in risks and benefits. *Maturitas* 2005; **52:** 1–10.
3. Baker VL. Alternatives to oral estrogen replacement: transdermal patches, percutaneous gels, vaginal creams and rings, implants, and other methods of delivery. *Obstet Gynecol Clin North Am* 1994; **21:** 271–97.
4. Jewelewicz R. New developments in topical estrogen therapy. *Fertil Steril* 1997; **67:** 1–12.
5. Yoo J-W, Lee CH. Drug delivery systems for hormone therapy. *J Control Release* 2006; **112:** 1–14.

Cardiovascular disorders. Observational studies have shown a decreased risk of ischaemic heart disease and consequent mortality in women receiving menopausal HRT and oestrogens are known to have some beneficial effects on the plasma lipid profile (see Effects on Lipids, above). However, results from randomised placebo-controlled studies of combined HRT for primary or secondary prevention of ischaemic heart disease have shown no overall benefit from HRT, and possibly an increased risk of coronary events (see Ischaemic Heart Disease, under Adverse Effects, above). It has therefore been recommended that HRT should not be used for prevention of cardiovascular disease.[1] Cardiovascular risk reduction, including management of blood lipids, is discussed on p.1164.

1. Mosca L, *et al.* Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation* 2004; **109:** 672–93.

Dementia. Several observational studies[1-3] have suggested that oestrogens can reduce the risk and delay the onset of Alzheimer's disease (p.362) in postmenopausal women receiving HRT. However, subsequent meta-analyses[4,5] concluded that studies conducted so far had substantial methodological problems and that results were conflicting. A further observational study[6] has also reported improved global cognition, and a slower rate of decline over 3 years in women receiving HRT. This study also found[7] that previous HRT use reduced the risk of developing dementia, but that current HRT use had no effect unless it was taken for more than 10 years. In contrast, another observational study (a substudy of the Nurse's Health Study[8] including 13 807 women) found no association between HRT use and cognitive performance over 2 years, and a suggestion that long-term use or initiation at older ages may increase the risk of cognitive decline. Any apparent benefits of HRT have also been thrown into question by the results of two large controlled studies of women who received conjugated oestrogens with medroxyprogesterone, or placebo, for about 4 years. At the end of the Heart and Estrogen/Progestin Replacement Study of women with coronary disease, there was no difference in cognitive function tests between those receiving HRT or placebo.[9] In the Women's Health Initiative Memory Study of over 4000 women aged 65 years and older, HRT had no clinically significant effect on global cognitive function, but the risk of suffering a substantial decline was higher for the HRT group.[10] Also, HRT did not prevent the development of mild cognitive impairment, and actually doubled the risk of dementia.[11] The absolute risk of dementia is small, however, and this increase is equivalent to 45 cases of dementia per year for every 10 000 women taking HRT compared with 22 cases for placebo. Similar effects were found for conjugated oestrogens alone in women with a prior hysterectomy who were studied in a separate arm of the Women's Health Initiative.[12,13] Pooling of data from both the oestrogen alone and combined HRT arms of this study suggested that HRT had an adverse effect on cognition,[13] increased the risk for both dementia and mild cognitive impairment, and should not be used to prevent dementia or cognitive decline.[12] A substudy of the Women's Health Initiative examined changes in specific cognitive domains, particularly memory and affect, in 1416 women given combined HRT or placebo.[14] After an average of 4 to 5 years, combined HRT had a negative effect on verbal memory, but a trend to a positive effect on figural memory; there was no significant influence on other cognitive domains and affect.

It has been suggested that age might provide an explanation for the conflict between results of observational and controlled studies. A review that compared results from controlled studies in younger women (less than 65 years old) and older women (65 or older) found that younger women may not be at risk from oestrogen alone and may benefit in verbal memory and attention.[15] However, the reviewer noted that there were limited data available on oestrogen alone in younger women and a lack of studies of combined HRT. A case-control study[16] has also reported a reduced risk of Alzheimer's disease in younger women (50 to 63 years old), but not older women, given HRT.

Some reports[17-19] suggest that treatment with oestrogens may be of benefit in women who already have Alzheimer's disease. However, in a controlled trial in women with mild to moderate Alzheimer's disease, oestrogen replacement therapy for one year did not slow the progression of disease or improve global, cognitive, or functional outcomes.[20] Further analysis of the range of hormone concentrations measured in this study[21] found no association between plasma concentrations of estradiol and estrone, and cognitive function.

1. Tang M-X, *et al.* Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996; **348:** 429–32.
2. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. *Arch Intern Med* 1996; **156:** 2213–17.
3. Kawas C, *et al.* A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology* 1997; **48:** 1517–21.
4. Yaffe K, *et al.* Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998; **279:** 688–95.
5. LeBlanc ES, *et al.* Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA* 2001; **285:** 1489–99.
6. Carlson MC, *et al.* Hormone replacement therapy and reduced cognitive decline in older women: the Cache county study. *Neurology* 2001; **57:** 2210–16.
7. Zandi PP, *et al.* Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache county study. *JAMA* 2002; **288:** 2123–9.
8. Kang JH, *et al.* Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. *Neurology* 2004; **63:** 101–7.
9. Grady D, *et al.* Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med* 2002; **113:** 543–8.
10. Rapp SR, *et al.* Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; **289:** 2663–72.
11. Shumaker SA, *et al.* Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; **289:** 2651–62.

12. Shumaker SA, *et al.* Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004; **291:** 2947–58.
13. Espeland MA, *et al.* Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004; **291:** 2959–68.
14. Resnick SM, *et al.* Women's Health Initiative Study of Cognitive Aging Investigators. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *J Clin Endocrinol Metab* 2006; **91:** 1802–10.
15. Maki PM. A systematic review of clinical trials of hormone therapy on cognitive function: effects of age at initiation and progestin use. *Ann N Y Acad Sci* 2005; **1052:** 182–97.
16. Henderson VW, *et al.* MIRAGE Study Group. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. *J Neurol Neurosurg Psychiatry* 2005; **76:** 103–5.
17. Ohkura T, *et al.* Long-term estrogen replacement therapy in female patients with dementia of the Alzheimer type: 7 case reports. *Dementia* 1995; **6:** 99–107.
18. Schneider LS, *et al.* Potential role for estrogen replacement in the treatment of Alzheimer's dementia. *Am J Med* 1997; **103** (suppl 3A): 46S–50S.
19. Asthana S, *et al.* High-dose estradiol improves cognition for women with AD: results of a randomized study. *Neurology* 2001; **57:** 605–12.
20. Mulnard RA, *et al.* Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. *JAMA* 2000; **283:** 1007–15. Correction. *ibid.*; **284:** 2597.
21. Thal LJ, *et al.* Estrogen levels do not correlate with improvement in cognition. *Arch Neurol* 2003; **60:** 209–12.

Hyperparathyroidism. The effects of HRT have been studied in postmenopausal women with mild primary hyperparathyroidism (p.1087). Oestrogens have been reported to reduce the rate of bone turnover and plasma concentrations of calcium in these patients, as well as increase bone mineral density.[1-4]

1. Marcus R, *et al.* Conjugated estrogens in the treatment of postmenopausal women with hyperparathyroidism. *Ann Intern Med* 1984; **100:** 633–40.
2. Selby PL, Peacock M. Ethinyl estradiol and norethindrone in the treatment of primary hyperparathyroidism in postmenopausal women. *N Engl J Med* 1986; **314:** 1481–5.
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Menopausal disorders. The menopause (p.2071) is a natural process that occurs in women with normal ageing. For some, the only noticeable change during the perimenopause is irregular menstrual periods that eventually stop, but for others vasomotor symptoms and atrophic vaginitis can cause significant discomfort; effects vary not only between women, but also for the individual woman as she progresses through the menopausal transition. Menopausal effects can be more sudden and intense in women who have the abrupt loss of oestrogen associated with menopause induced by surgery, chemotherapy, or radiotherapy. Many reviews and guidelines have been published on management of the menopause including the use of HRT.

Acute menopausal symptoms. There are a number of strategies that may be tried for the management of acute menopausal symptoms.

- In postmenopausal women with only *vaginal symptoms*, non-hormonal vaginal lubricants and moisturisers can be tried first.[1] If these are inadequate, locally-acting vaginal oestrogen therapy may be effective;[1,2] improvement typically occurs within a few weeks, but may take 4 to 6 weeks. Oestrogen therapy may continue for as long as required for symptomatic relief, but data on the effects of long-term use are lacking.[1] Systemic exposure from vaginal preparations is believed to be limited, and the addition of a progestogen to protect against endometrial hyperplasia in women with a uterus is generally not indicated when low-dose local oestrogen therapy is used.[1] Nevertheless, studies have reported cases of endometrial hyperplasia and overstimulation; a systematic review found that there were insufficient data to confirm whether a progestogen should be given when vaginal oestrogens are used for more than 6 months.[2] Women using a cream may be at higher risk of systemic absorption since dosing relies on the amount of cream measured by the woman, which may be variable compared with vaginal tablets. (Some vaginal preparations are designed to deliver sufficient systemic oestrogen to treat vasomotor symptoms—see below.)
- Mild *vasomotor symptoms* may be adequately managed with lifestyle changes such as maintaining a lower core body temperature, physical activity, and relaxation techniques.[3] Moderate to severe symptoms can be controlled with HRT,[3-9] usually given orally or transdermally; some vaginal rings also deliver sufficient oestrogen to the circulation to treat vasomotor symptoms. The lowest dose that controls symptoms is given short term, generally for no more than 5 years. Women without a uterus, and who have not had endometriosis, may receive continuous oestrogen alone.[6,7] Women with a uterus should also receive a progestogen to reduce the risk of endometrial hyperplasia and cancer associated with unopposed oestrogen therapy[3,4,6,9] (for a discussion of the risks of endometrial cancer with HRT, see under Adverse Effects, above). In women who are postmenopausal (more than 12 months) continuous combined HRT may be used.[7] However, continuous combined HRT can cause irregular bleeding in perimenopausal women, so they are usually given a cyclical progestogen orally or transdermally, which will cause regular withdrawal bleeding; an alternative is the levonorgestrel intrauterine device. Vaginal progesterone or oral long-cycle regimens (progestogen for 12 to 14 days every 3 to 6 months) have been used to reduce adverse effects, but it is not clear that these provide adequate endometrial protection.[9]

  Perimenopausal women are still potentially fertile and HRT does not provide contraception. It is now considered that women free of all risk factors for venous and arterial disease may use a low-dose combined oral contraceptive (p.2069) to provide both relief of menopausal symptoms and contraception.[3] However, it is recommended that they should stop the oral contraceptive at the age of 50, so that the menstrual cycle and menopausal status can be assessed. Non-hormonal contraceptives or the progestogen-only oral contraceptive (see p.2070) may be used if contraception is required in perimenopausal women using HRT, and continued to the age of 55 when natural sterility can be assumed.[10]

  Alternative hormonal therapies for vasomotor symptoms include the progestogens megestrol and medroxyprogesterone.[3,6,11] Tibolone, which has oestrogenic, progestogenic, and androgenic properties, is another option for postmenopausal women.[4,7,12,13]

  Non-hormonal therapies have also been tried although evidence for the efficacy of these is less conclusive than that for HRT.[3,6,11,14] The antidepressants fluoxetine, paroxetine, and venlafaxine have shown some benefit in small trials, and low doses of gabapentin have been reported to be effective. Clonidine or veralipride may be considered when HRT is not suitable, but the use of these can be limited by adverse effects. Other therapies have been used to manage vasomotor symptoms based on anecdotal reports of benefit, but they have generally not been effective when studied in placebo-controlled trials. These include isoflavones from soya or red clover, evening primrose oil, cimicifuga (black cohosh), *Angelica sinensis* (dong quai), and vitamin E.
- *Non-specific symptoms* may also improve in women given HRT, but good evidence is somewhat scanty and HRT should not be used solely for these indications. Oestrogens might reduce recurrent urinary-tract infections in susceptible women,[7] but incontinence can worsen (see below). Many women report improved mood and well-being when given oestrogens, although it is unclear to what extent this is due to relief of other symptoms. Two large controlled studies[15,16] have found that combined HRT improved some quality of life measures in postmenopausal women with vasomotor symptoms, but that asymptomatic women in general received no benefit. There is insufficient evidence to support the use of oestrogen, alone or in combined HRT, for the treatment of depression.[9] Moreover, the addition of progestogens carries some risk of adverse effects on mood such as depression, anxiety, and irritability. Androgens such as testosterone are sometimes used as adjuncts to HRT to improve psychological well-being and libido,[17] particularly in women with surgically-induced menopause.[6]

Initiation of HRT. There is increasing discussion about when to start HRT, as the timing of treatment after menopause seems to relate to long-term health outcomes. There has been interest particularly in how the effect of HRT on ischaemic heart disease might be affected by age, considering that many women who took part in studies of HRT were older than those who generally take HRT for vasomotor symptoms in their 50s (see Ischaemic Heart Disease under Effects on the Cardiovascular System, above). The benefit-risk ratio is more likely to be acceptable for short-term symptomatic management in younger women around the age of typical natural menopause (about 51 years). It is also now generally advised that, unless there is a compelling indication, HRT should not be started in women older than 60 who have had a natural menopause at the typical age because they will usually have higher baseline risks of cardiovascular disease and breast cancer.[9] It is also generally agreed that all women who have had a *premature natural or induced menopause* should be offered HRT or a combined oral contraceptive until about 50 years of age, unless there are specific contra-indications to therapy. These women may need higher doses of HRT than those normally used to control vasomotor symptoms. Adjunctive androgen therapy may also be considered, particularly in oophorectomised women.[18] Considerations as to how long they need to continue HRT after the usual age for the menopause are probably the same as for other women.

Long-term use of HRT. There are extensive data from observational studies on the beneficial effects on fracture rates and cardiovascular disease, on the risks for development of breast cancer and endometrial cancer, and on the possible effects on overall mortality. However, the women receiving HRT in these studies may differ from women not receiving HRT, and the extent of any bias resulting from this is unclear.[19] Randomised prospective studies have confirmed the increased risk of breast cancer, venous thromboembolism, stroke, and dementia associated with combined HRT (see under Adverse Effects, above). Contrary to the anticipated benefits for preventing ischaemic heart disease, these studies also found an increase in coronary events, and such use is now not recommended (see Cardiovascular Disorders, above). These results have led to recommendations that HRT should not be used long term solely for the prevention of chronic disease in generally healthy postmenopausal women.[6,20,21] However, although other treatments are now preferred for the prevention and treatment of osteoporosis (p.1084), long-term HRT may be suitable for some women (see also below).

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Osteoporosis. Oestrogens may be used in selected patients for the treatment and prevention of postmenopausal osteoporosis (p.1084). They have a direct antiresorptive effect on bone, and will increase bone mass density (BMD). However, data from the Heart and Estrogen/Progestin Replacement Study (HERS) have called into question the benefit of HRT in reducing the incidence of fractures.[1,2] A meta-analysis[3] including the initial HERS data,[1] most of which were from women without osteoporosis, consequently found only non-significant reduction in fracture risk in older women although overall the risk of fracture was reduced by between 20 and 30%. Subsequent results from the Women's Health Initiative[4] showed that, contrary to the results of this meta-analysis, combined HRT did reduce the risk of fracture in healthy postmenopausal women. Similarly, cohort data from 138 737 women in the Million Women Study[5] showed that current use of HRT reduced fracture risk, but that this protection wore off rapidly after stopping HRT. Other studies have also reported that protection against loss of bone mineral density[6] and fracture[7] is not retained after stopping HRT.

Despite the probable benefits, there is substantial evidence to show that HRT is associated with an increased risk of cancer, particularly breast cancer (see Breast under Carcinogenicity, above), and some cardiovascular diseases such as stroke and venous thromboembolism (see Effects on the Cardiovascular System, above). It is now generally recommended by authorities, such as the UK CSM,[8] that the risk to benefit ratio of HRT is unfavourable for the prevention of osteoporosis as first-line therapy, and that it should not be used in this way for women over 50 years of age. HRT does, however, remain an option when other osteoporosis prevention therapies are unsuitable. Younger women who have experienced premature menopause may be given HRT for menopausal symptoms and to prevent osteoporosis until the age of 50, after which its use should be reviewed and considered a second-line choice.

Suggested minimum daily doses are 625 micrograms of oral conjugated oestrogens, 2 mg of oral estradiol or 50 micrograms transdermally, and 15 micrograms of oral ethinylestradiol; lower doses may also be effective,[9-15] and a transdermal patch supplying 14 micrograms of estradiol daily is licensed for the prevention of osteoporosis in the USA. Addition of a progestogen (required to prevent endometrial hyperplasia in women with a uterus) does not impair the beneficial effect of oestrogens on BMD, whether given cyclically or continuously,[16,17] and may provide a further reduction in risk of fractures.[18] Although current, long-term use of HRT can increase BMD and reduce fracture risk, unresolved issues are the duration of therapy required to prevent fractures in old age, and the ideal age to start therapy to obtain the maximum benefits to the bone with the minimum risk of breast cancer.[18-20]

Oestrogens may also be used in women to reduce the risk of corticosteroid-induced osteoporosis (see Effects on Bones and Joints, p.1491).

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Urinary incontinence. Urinary incontinence (p.2180) may be one of a number of acute symptoms associated with a decline in oestrogen levels at the menopause (see Menopausal Disorders, above). Studies[1,2] suggest that oestrogens used with alpha-adrenoceptor agonists are effective in the management of female stress incontinence and this combination has been advocated for use in postmenopausal patients with mild symptoms. Unfortunately addition of a progestogen to treatment to reduce the risk of endometrial carcinoma in women with an intact uterus might exacerbate the incontinence.[3] The value of oestrogens used without an alpha-adrenoceptor agonist in urinary incontinence is less clear. One study[4] reported that oestrogen therapy and pelvic floor exercises for 18 months was more effective than exercises alone in women with mild stress incontinence. However, a placebo-controlled study[5] found no improvement after 6 months of oestrogen therapy.

Some consider that oestrogens may be of use for symptoms of urgency, frequency, and nocturia in postmenopausal patients with urge incontinence, particularly if given locally;[6] it has been suggested that hypoestrogenism may reduce the sensory threshold of the bladder.[7] A meta-analysis of 23 studies concluded that oestrogen therapy subjectively improved urinary incontinence in postmenopausal women but many of the studies examined were considered to be deficient in some respect.[8] Later well-designed studies[9,10] of women with stress, urge, or mixed incontinence found that HRT did not improve, or even worsened, measures of incontinence, although there was the possibility that concomitant progestogen therapy might have affected efficacy. Furthermore, the placebo-controlled Women's Health Initiative[11] found that both oestrogen alone and combination HRT increased the overall risk of developing stress, urge, or mixed incontinence, and worsened incontinence in women who were symptomatic before starting HRT. Another placebo-controlled study[12] also found that combination HRT increased the risk of developing stress or urge incontinence, and the large Nurses' Health Study cohort reported[13] that the current use of HRT increased the risk of developing urinary incontinence.

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Gonad-regulating Hormones

The Hypothalamic-Pituitary-Gonadal Axis

The regulation of sexual function involves the so-called hypothalamic-pituitary-gonadal axis.

The pituitary gland or hypophysis is composed in humans of 2 parts, the anterior lobe or adenohypophysis, and the posterior lobe (neurohypophysis) and neural stalk, above which lies the hypothalamus. Both parts of the pituitary secrete hormones: posterior pituitary hormones are synthesised in the hypothalamus and transported down nerve fibres to the pituitary where they are stored until required, whereas anterior pituitary hormones are synthesised *in situ* by specialised cells, but are subject to complex hormonal control by hypothalamic regulatory hormones and target organ hormones, as well as excitatory and inhibitory impulses from the brain. These interacting systems are collectively known as the hypothalamic-pituitary-endocrine axes.

The anterior pituitary hormones follicle-stimulating hormone (FSH) and luteinising hormone (LH) are collectively known as **gonadotrophic hormones** or gonadotrophins. They are glycoproteins secreted by specialised pituitary cells (gonadotropes) that stimulate gonadal function and sex hormone production. In men, LH stimulates the synthesis of testosterone and other androgens, while in women, FSH and LH regulate production of oestradiol and synthesis of progesterone in a complex and interacting manner. A third substance with gonadotrophic (primarily luteinising) actions, chorionic gonadotrophin, is secreted by the placenta.

The synthesis and secretion of pituitary gonadotrophic hormones is in turn stimulated by a hypothalamic releasing hormone, **gonadotrophin-releasing hormone** (GnRH). In post-pubertal subjects, GnRH is secreted from the hypothalamus at regular intervals determined by an internal 'clock' or neuronal pulse generator in the arcuate nucleus, and enters the blood of the portal vascular system that links the hypothalamus to the anterior pituitary. This results in pulsatile release of the gonadotrophic hormones, which is essential for normal gonadal function. More prolonged and continuous exposure to GnRH leads to desensitisation and downregulation of its receptors on pituitary gonadotropes, and hence, after an initial surge, to suppression of gonadotrophic hormone secretion.

The sex hormones themselves produce negative feedback effects at both hypothalamic and pituitary levels. In general, both oestrogen and progesterone reduce the amplitude (i.e. the amount) of gonadotrophic hormone released; progesterone also reduces the frequency of the pulses. Testosterone is thought to act by conversion to oestrogen via aromatase, although it also has some direct action. The gonads also produce a hormone, inhibin, that selectively inhibits FSH secretion from the pituitary without affecting LH, and its biological opposite, activin, which stimulates pituitary FSH secretion.

Types of Gonad-regulating Hormone

Gonad-regulating hormones in clinical use may be divided into 3 major groups.

- Endogenous follicle-stimulating and luteinising hormones are available from urinary sources as human menopausal gonadotrophins or menotrophin (p.2109) and as urofollitropin (p.2136), and in recombinant forms such as follitropins alfa and beta (p.2104) and lutropin alfa (p.2112). Chorionic gonadotrophin and its recombinant form choriogonadotropin alfa (p.2085) are also used.
- The hypothalamic releasing hormone gonadorelin (p.2106), and its longer-acting analogues such as buserelin (p.2083), deslorelin (p.2093), goserelin (p.2108), histrelin (p.2109), leuprorelin (p.2111), nafarelin (p.2117), and triptorelin (p.2135) are widely used to stimulate or inhibit the hypothalamic-pituitary-gonadal axis.
- More recently, direct gonadotrophin-releasing hormone antagonists have become available, such as abarelix (p.2081), cetrorelix (p.2084), and ganirelix (p.2105).

Use of Gonad-regulating Hormones

The gonad-regulating hormones play an important role in the management of a number of endocrine disorders, as discussed in the reviews below and elsewhere in this chapter. They also play an important role in the management of endocrine-sensitive malignant neoplasms (see p.643).

Amenorrhoea

Amenorrhoea is the absence of menstruation: a break in menstruation of 6 months or more is considered pathological in an adult woman who is not pregnant, lactating, or menopausal. Amenorrhoea occurring from the time of puberty is known as primary, while amenorrhoea developing later in life is referred to as secondary. Pathological amenorrhoea is usually associated with infertility (see also below). Hirsutism (p.2089) may also be present.