The number of women in Britain using hormone replacement therapy (HRT) is steadily increasing, from an estimated 2% of women aged 40–64 yr in 1987, to 22% in 1994. The projected figure for this age group in the year 2000 is 25%. This increase does not take into account older women who continue to use HRT. Figures from the US suggest a considerably greater use of HRT (42.5% current users, and 20.9% past users in a telephone survey of 1082 randomly selected women). Interestingly, this survey concluded that a large proportion of women felt inadequately informed about the risks and benefits of HRT. As women and their general practitioners become well informed about the potential benefits of HRT, as well as the perceived risks, use may rise more rapidly than projected. The percentage of the population of post-menopausal age is increasing, and the absolute number of HRT-using women presenting for surgery, both elective and emergency, will increase substantially. It is, therefore, relevant for the anaesthetist to be aware of the effects of HRT. Unfortunately, despite the widespread and increasing use of HRT, there are surprisingly few randomized controlled trials (RCTs) investigating its effects; most information derives from numerous observational studies.

What types of HRT are used?
HRT is a generic term, and encompasses the use of unopposed oestrogen therapy, and combinations of oestrogens and progestogens. Unopposed oestrogens are generally used only in women who have had a hysterectomy, because of the associated high rate of endometrial hyperplasia. Cyclical use of progestogens have the disadvantage for patients of producing cyclical withdrawal bleeding, which can be avoided by continuous use of the drug. HRT may be administered orally, transdermally, or as a subcutaneous implant.

The oestrogen and progesterone used for HRT are structurally different chemicals than those used in the oral contraceptive pill, and are of lower potency. The doses of oestrogen (as 17ß-oestradiol) in transdermal patches and of conjugated equine oestrogen in oral preparations of HRT are approximately one-sixth as potent as the ethinyl oestradiol used in oral contraceptives. The doses used in HRT are designed to restore oestradiol levels to the lower end of the normal pre-menopausal range. This contrasts with the oral contraceptive pill which is designed to suppress the natural ovulatory cycle.

Studies differ in their conclusions about the relative importance of the different HRT regimens in current use. Some studies investigating the effects of HRT do not differentiate between the different preparations available. Further work is needed to address this issue. Finally, there is still relatively little work on the newer drugs such as tibolone, which is a synthetic compound with oestrogenic, progestogenic, and androgenic properties.

Indications for HRT
HRT helps to alleviate the unpleasant symptoms associated with the menopause. RCTs have demonstrated the efficacy of HRT in relieving hot flushes, night sweats, and vaginal dryness. A recent meta-analysis has also confirmed that HRT reduces the depressed mood associated with the menopause.

Considerable interest has been generated by the more long-term potential benefits of HRT therapy, which include a possible reduction in morbidity and mortality from cardiovascular disease (both coronary heart disease and stroke), reduction in morbidity and mortality associated with osteoporosis, and reduction in the cutaneous ageing process. However, there are also potential hazards of HRT therapy. Reported adverse effects include increased risk of malignant disease (specifically breast cancer) and increased risk of venous thromboembolism.

These issues are relevant for the anaesthetist, and an understanding of them will help rationalize the periopera-
HRT and venous thromboembolism

Several large studies have consistently demonstrated an increased risk of venous thromboembolism in women using HRT. This risk appears to be restricted to the first year of HRT use, and is estimated at 2–3 times that of non-HRT users. These figures have been confirmed in a recent meta-analysis of relevant studies. It is important to appreciate that although a 2- to 3-fold increase in risk appears high, this only represents one or two additional cases of venous thromboembolism per 10 000 women per year. This increase in risk is still not universally accepted.

Mechanism of increased risk of venous thromboembolism

It is recognized that there are both congenital and acquired risk factors for thromboembolic disease, and that these are both exogenous and endogenous. The Thromboembolic Risk Factors Consensus Group (THRIFT) has published a widely accepted list of both groups of risk factors. HRT affects haematological variables relating to coagulation and fibrinolysis; these are summarized in Table 1.

<table>
<thead>
<tr>
<th>Measure of coagulation/ fibrinolysis</th>
<th>Effect of HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin production</td>
<td>Dose-dependent increase</td>
</tr>
<tr>
<td>Thrombin activity</td>
<td>Dose-dependent increase</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>Decreased</td>
</tr>
<tr>
<td>Protein S antigen</td>
<td>Decreased</td>
</tr>
<tr>
<td>Factor VII coagulant activity</td>
<td>Increased in oestrogen only preparations</td>
</tr>
<tr>
<td>Factor VII antigen</td>
<td>Increased</td>
</tr>
<tr>
<td>Plasma fibrinogen</td>
<td>Decreased</td>
</tr>
<tr>
<td>Protein C</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Inherited thrombophilias

There is a growing body of opinion, which suggests that women who develop venous thromboembolism whilst taking HRT have an underlying thrombophilic tendency that may act additively with a direct effect of oestrogen on the coagulation system.

Inherited thrombophilic defects can be broadly classified as antithrombin deficiencies, or abnormalities of the protein C-protein S system. The prevalence of inherited thrombophilias varies between 1 in 500 for protein C deficiency, to up to 1 in 14 for Factor V Leiden mutation. Current research suggests that in many cases inherited thrombophilia is not a single but a multi-gene defect. There may well be further, as yet undetectable genetic variants associated with increased risk of venous thromboembolism occurring in relatives of women with proven defects.

The prevalence of thrombophilic abnormalities in an asymptomatic population has been estimated at 6.2%, but this rises to 60.2% in patients presenting with venous thromboembolism who have a personal or family history of venous thromboembolism. It has, therefore, been suggested that patients with a personal or family history of venous thromboembolism should be routinely screened for inherited thrombophilic defects. The financial implications of such a policy would be considerable. In an attempt to determine the potential benefits of routine screening, a recent study has investigated the interactions between HRT use and risk of venous thromboembolism in women with and without pro-thrombotic states. The key findings of the study are shown in Table 2.

This study concludes that the combination of HRT use and thrombophilias (especially if multiple) increases the risk of venous thromboembolism ‘substantially’ (13-fold in the case of women with APC resistance). The authors suggest that it is reasonable to offer coagulation screening to women with a past or family history of venous thromboembolism, and advise that women who are discovered to have an inherited thrombophilia should be counselled about the increased risk before prescription of HRT.

Acquired thrombophilias

Acquired thrombophilias are, by definition, associated with increased risk of thrombosis. The most common cause of acquired thrombophilia is antiphospholipid syndrome, which may occur in isolation, or in association with systemic lupus erythematosus (SLE). There have been small observational studies suggesting that HRT can be safely used in patients with inactive, stable, or moderate disease; a large prospective double-blind placebo-controlled study (Safety of Estrogens in Lupus Erythematosus—National Assessment) is also in progress which should enable definitive evidence-based recommendations to be made. Both antiphospholipid syndrome and oestrogen therapy are quoted risk factors in the THRIFT guidelines, and it would, therefore, seem sensible to use thromboprophylaxis in all women presenting for surgery who have SLE irrespective of whether they are receiving HRT.

Mode of administration of HRT

A recent study suggests that the risk of venous thromboembolism may be related to the mode of administration of
HRT. The findings demonstrated increased prothrombin activation peptide and decreased antithrombin activity in women receiving oral oestrogens, but not in those receiving transdermal preparations. This difference between transdermal and oral oestrogen preparations has been confirmed in a recent review, but contradicted in another study which demonstrated significant changes in thrombophilia profile associated with the administration of transdermal oestradiol, and concluded that these changes paralleled those observed with oral HRT.

The exercise habits and fat distribution of women may be as important as HRT use in determining risk of venous thromboembolism. Plasma fibrinogen levels are reduced in physically active women regardless of HRT use. However, a study that controlled for the effects of age, smoking, body mass index and the use of diuretics demonstrated decreased fibrinogen levels and decreased plasma viscosity values in women receiving both unopposed oestrogens and combination therapy.

The possible effect of HRT on arterial thrombosis has not been reported in humans, but in a recent study in monkeys there was no increased risk of occlusive thrombus following a standardized stenosis/injury procedure to the carotid artery. This finding may be relevant when considering the relevance of thrombotic risk following surgery.

Current recommendations for women receiving HRT and undergoing surgery

Unfortunately, there is no evidence base for any of the current recommendations concerning pre- and perioperative management of women using HRT (Table 3). In practice, many women admitted for intermediate or major surgery (especially those presenting for gynaecological surgery) will have additional risk factors that mandate the use of thromboprophylaxis.

The lack of clear guidance reflects the current state of knowledge about pre-operative prediction of post-operative DVT. One recently published RCT suggests significantly increased risk of thromboembolic events following lower extremity fractures and for 90 days after in-patient surgery in women with coronary heart disease taking HRT compared with a control group of non-HRT users. The THRIFT and other studies offer clinical guidelines for identification of patients at risk of venous thromboembolism. However, at present the clinical utility of pre- and post-operative haemostatic tests that predict post-operative deep vein thrombosis remains unproven.

### Issues of relevance to the anaesthetist

If there is an increased rate of idiopathic venous thromboembolism for women in the first year of HRT therapy these women are presumably also at increased risk of perioperative venous thromboembolism during this time. The following questions are relevant.

**Is the magnitude of increased risk quantifiable?**

There is now consistent data suggesting a 3- to 4-fold increase in relative risk of venous thromboembolism in all women during the first year of taking HRT. The absolute risk of venous thromboembolism for any individual woman will be influenced by other additional risk factors. The only published evidence currently available suggests a substantial (but variable according to particular abnormality) further increase in risk of venous thromboembolism for women with underlying prothrombotic states.

**Does the risk versus benefit balance favour stopping HRT pre-operatively?**

The decision to stop medication pre-operatively implies that the risks of continuing a drug outweigh the risks of stopping it. This debate has been extensively rehearsed in the case of the oral contraceptive pill, where it is clear that the potential risks of stopping the ‘Pill’ pre-operatively include unwanted pregnancy, the effects of surgery and anaesthesia on that pregnancy, the risks of therapeutic abortion, and the risks of pregnancy itself. The risks of stopping HRT are considerably less dramatic, but equally the risks of continuing it are undefined. This applies particularly to women whose...
proposed surgical procedure would place them in a high-risk category for venous thromboembolism independent of HRT use. Recent guidelines from the Royal College of Obstetricians and Gynaecologists state that there is no evidence to support a policy of routinely stopping HRT before surgery, and that patients with oestrogen implants should be advised that they must not discontinue their cyclical progestogen.21

Should perioperative mechanical and/or pharmaceutical thromboprophylaxis be used?

Clinical guidelines suggest the use of graduated compression stockings for patients at low risk of venous thromboembolism. For patients at moderate or high risk of venous thromboembolism, RCTs strongly recommend the use of prophylactic heparin perioperatively.33 A recent review of the prevention and treatment of venous thromboembolism consistently recommends the use of low molecular weight heparin prophylaxis for elective hip or knee replacement surgery, and for hip fractures, but does not mention HRT as an additional risk factor.26

There is good evidence that administration of either low molecular weight heparin or suitable doses of oral anticoagulants pre-discharge reduces the relative risk of DVT following hip surgery by about 50%.7 Many women receiving HRT and undergoing surgery will, therefore, receive prophylactic heparin regardless of HRT use.

The decision to use prophylactic heparin in women receiving HRT who would otherwise be in a low risk group cannot at present be made on the basis of RCT evidence, but remains a clinical judgement.

The question of need for ongoing prophylaxis against venous thromboembolism has not been extensively debated in the literature either, despite an awareness of the frequency of late symptomless DVT after total hip replacement. The recent publication of the results of the Pulmonary Embolism Prevention trial, and an accompanying editorial, suggest the need for further research into the role of low dose aspirin for post-hospital discharge thromboprophylaxis.43 47 It would seem sensible for such research to also consider the use of low dose aspirin for women receiving HRT.

Use of any perioperative pharmacological thromboprophylaxis carries a risk of increased surgical bleeding and subsequent morbidity. Interpretation of published data and clinical decision-making must include consideration of these risks.10

HRT and cardiovascular disease

Data from numerous epidemiological studies consistently suggest that the risk of coronary heart disease is reduced by up to 50% by oestrogen replacement therapy. The mechanisms for this have not been fully elucidated. Moreover, the Heart Estrogen Replacement Study (HERS) has founded the epidemiological data by suggesting that in post-menopausal women with established coronary heart disease there is a trend towards increased risk of cardiovascular disease in the first year of HRT treatment.27 There has also been controversy about whether the addition of progestogens in combination HRT preparations reduces the benefits of oestrogen therapy, although a large epidemiological study has suggested that combined preparations confer even more benefit than oestrogens alone.37 A recent review of published RCTs has concluded that whilst HRT improves surrogate measures of risk of atherothrombosis, adverse effects on biological mechanisms related to risk cannot be excluded.52

Effects of HRT on lipoproteins

Lipoprotein profile appears to be an important determinant in development of cardiovascular disease. In women, high-density lipoprotein cholesterol (HDL-C) has been shown to have a strong inverse relationship to heart disease risk2 and observational studies suggest that increasing HDL-C is accompanied by a reduction in heart disease risk. (It is, however, important to note that there have been no specifically directed RCTs to confirm this.) Oestrogen has been consistently demonstrated to increase HDL-C in post-menopausal women, and is therefore considered to be one of the most important mechanisms by which HRT confers cardioprotection. A recent major multi-centre prospective randomized trial concluded that both unopposed oestrogen and various oestrogen–progesterone combination therapies improved lipoprotein profiles and lowered plasma fibrinogen levels.59

Several studies demonstrate that HRT reduces low density lipoprotein cholesterol (LDL-C), but the significance of this in relation to cardiovascular risk is unknown. Similarly, effects of HRT on plasma triglyceride levels are inconsistent between studies, and their relevance is not clear.

Effects of HRT on arterial physiology

Progressive arterial endothelial damage occurs with increasing age, and this predisposes to atherosclerosis. Studies on the carotid artery have investigated the effects of HRT. The media layer of the carotid artery wall contains high levels of collagen types I and III. A thick, healthy media is necessary for maintenance of a healthy intimal layer of the vessel wall. In post-menopausal women, the media layer becomes thin (as a result of collagen depletion), allowing the intimal layer to thicken, which predisposes to formation of atheromatous plaques. Use of HRT encourages thickening of the media and delays progression of atheromatous change.1

von Willebrand factor, soluble thrombomodulin, and tissue plasminogen activator are all significantly reduced after 6 weeks of HRT. These are markers of endothelial function, and therefore provide further evidence to support
HRT and anaesthesia

the beneficial effects on the cardiovascular system of HRT.\(^3\)

A further study of carotid wall thickness in diabetic and non-diabetic HRT users confirmed the potentially beneficial effect of HRT in both groups.\(^{14}\)

Another indirect measure of atherosclerosis is systemic arterial compliance—atherosclerotic arteries will be stiffer, and cause a decrease in systemic compliance. HRT (oestrogen or oestrogen–progesterone) has been shown to significantly increase total systemic arterial compliance in both smokers and non-smokers.\(^{35}\)

The study of carotid and radial artery tonometry in women taking HRT compared with non-treatment control groups has demonstrated a reversal of age-related arterial stiffening in HRT users.\(^{24}\)

Using another indirect measure of arterial compliance (flow-mediated dilatation in response to reactive hyperaemia), HRT (oestrogen alone or a combined preparation) appears to be protective. Dilatation was decreased compared with pre-menopausal women, but to a significantly lesser extent than in post-menopausal women not using HRT.\(^{34}\) These findings have been confirmed in a study investigating peripheral vascular flow velocity in post-menopausal women using HRT (oral oestrogen, oestrogen patch, or combined oestrogen–progesterone) compared with a no treatment control group. Peripheral vascular flow velocities were increased in all HRT groups.\(^{30}\)

These studies support suggestions that HRT has a beneficial effect on blood pressure. Although such an effect has not been consistently demonstrated, this may be a reflection of study design. A recent study has demonstrated significant decreases in both systolic and diastolic ambulatory blood pressures compared with a control group after 1 year of HRT. However, these changes were not revealed by ‘office’ blood pressure measurement.\(^{53}\)

Proudler, who examined the effect of combined oestrogen–progesterone HRT on angiotensin-converting enzyme (ACE) activity, has proposed a further mechanism for the cardioprotective effects of HRT. Serum ACE activity was significantly reduced in treated women compared with untreated controls.\(^{42}\)

HRT and cardiac function

Several studies have suggested that HRT has a directly beneficial effect on cardiac performance. In one prospective study of combined HRT for 6 months, echocardiographic measurement of left ventricular ejection fraction was significantly increased in the HRT group compared with control, and there was significant improvement in diastolic function.\(^{48}\) A similar study investigated the effect of HRT on left ventricular diastolic function in both normotensive and hypertensive women before and during treatment, and found significant improvement in several parameters (assessed by echocardiography) of diastolic function in both groups of women after 12 months of HRT.\(^{3}\)

HRT and cerebrovascular accident

Most studies report a reduction in death rate from stroke in HRT users. However, the data are less consistent than those relating to death from coronary heart disease, and at least one large prospective study has failed to demonstrate any influence of HRT (either unopposed oestrogens or combination therapy) on the risk of non-fatal haemorrhagic or thromboembolic stroke.\(^{40}\)

What is the relevance of these findings for the anaesthetist?

Until there is more direct RCT evidence it is unlikely that women will be prescribed HRT for the sole purpose of secondary prevention of coronary heart disease.\(^{56}\) HRT has effects on cardiovascular physiology that are of uncertain clinical significance. The anaesthetist should be aware of this area of ongoing research; if the potentially cardioprotective effects of HRT are confirmed this would be an important factor in determining the balance of risks and benefits of continuing perioperative use of HRT.

HRT and osteoporosis

Accelerated bone loss in post-menopausal women is well documented, and it is known that this can be prevented by treatment with oestrogens. Untreated osteoporosis is a significant problem; fractured neck of femur accounts for 20% of all orthopaedic bed occupancy in the UK, and 16% of women with fractured neck of femur die as a direct consequence of the fracture.\(^{57}\) Despite this, controversy continues about the most appropriate treatment, and the duration of benefit of HRT therapy. HRT reduces bone turnover and increases bone mineral density, and it appears that addition of progestogens to oestrogen therapy does not reduce these effects. The protective effect of HRT declines rapidly following cessation of treatment, and the lowest dose of HRT that prevents fracture is unknown. It has been suggested that long-term use of HRT is associated with a 30–50% reduction of hip, spine, and wrist fractures.\(^{8}\) However, there are other factors associated with development of osteoporosis, and few of the studies of HRT and osteoporosis have been of sufficiently rigorous design to account for the many potentially confounding variables affecting the antifracture efficacy of the drugs being investigated.\(^{46}\)

A recent epidemiological study of more than 11 000 women found that those using HRT were more likely to have a high level of education, take more physical exercise, and have a higher intake of dietary fibre. The study concludes that caution is required in interpreting observational studies of HRT effects, since selection bias may operate.\(^{41}\)
**Table 4** Relationships between HRT use and risks of malignant disease. (OR=odds ratio, CI=95% confidence interval)

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Risks of HRT use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cancer</td>
<td>Increased risk with unopposed oestrogen therapy; possible slight increase in risk (not quantified) with combined HRT preparations</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Increased risk: OR 1.15 (CI 1.05–1.27)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Increased risk in current HRT users, proportional to duration of use</td>
</tr>
<tr>
<td>Breast cancer (risk reduction)</td>
<td>Significant reduction in mortality if HRT has ever been used</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Reduced risk if HRT has ever been used: OR 0.64 (CI 0.46–0.88)</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>Reduced risk if HRT has ever been used: OR 0.46 (CI 0.29–0.72)</td>
</tr>
</tbody>
</table>

**HRT and malignant disease**

There has been concern that the benefits of HRT may be outweighed by an increased risk of developing malignant disease. The conclusions of recent studies are summarized in Table 4.

Whilst the associations (both positive and negative) between HRT and malignant disease currently have no direct impact on the work of anaesthetists, it is possible that further research in this field may change the pattern of surgical practice for malignant disease in the future.

**Conclusions**

Numerous questions about HRT remain unanswered. Current research indicates that there are potentially enormous benefits of HRT on morbidity and mortality of postmenopausal women, and its use is likely to increase. As with the oral contraceptive pill, many women may not regard HRT (particularly when used as a topical patch or subcutaneous implant) as medication, and may fail to disclose HRT use unless specifically asked by the anaesthetist.

Although there is clear evidence from RCTs that use of HRT is associated with a small increase in relative risk of venous thromboembolism, there is no such evidence to demonstrate any increased risk of peri-operative venous thromboembolism in HRT users. Current advice (based on limited evidence and expert opinion rather than on the results of RCTs) is that HRT use should be regarded as one of the risk factors for venous thromboembolism to be considered when assessing patients pre-operatively. There is no evidence to support stopping HRT pre-operatively. Use of mechanical or pharmacological methods of thromboprophylaxis is recommended for women taking HRT; the choice of thromboprophylaxis will depend upon the number of risk factors for venous thromboembolism.

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