13 Women with comorbidities

At a glance

- Fibroid volume decreases by up to 40% at the menopause, attenuated by hormone replacement therapy (HRT), which may cause some fibroid growth.
- Endometriosis is an estrogen-dependent disease, regressing at the menopause, which could potentially be re-stimulated by HRT.
- Women with polycystic ovary syndrome need careful monitoring for cardiovascular disease, owing to their increased prevalence of metabolic abnormalities.
- Estrogen replacement has a beneficial effect on cholesterol profiles and the risk of developing type 2 diabetes.
- All women should have their personal risk of venous thromboembolism assessed prior to commencing HRT.
- No increased risk for venous thromboembolism has been noted with transdermal HRT, even in women with known thrombophilias.
- Abdominal obesity is associated with an increased risk of cardiovascular disease, type 2 diabetes, cancers and overall mortality.
- Hypothyroidism is common in women over 60, so screening for thyroid-stimulating hormone level in women with risk factors for thyroid disease is warranted.
- Migraine with aura is not a contraindication to HRT.
- Women with rheumatological and connective tissue diseases predisposing to osteoporosis may gain additional bone protective benefit from HRT.

Introduction

Estrogen receptors are widespread throughout the body. Consequently, during the menopausal transition, changing estrogen levels can influence a wide variety of organs and can potentially impact on the course and

management of coexistent medical conditions. These conditions require careful evaluation by health professionals when advising a woman about her risks and before starting a woman on hormone replacement therapy (HRT) or other medication.

Gynaecological disorders

Fibroids

Any symptoms related to fibroids are likely to improve or disappear around the menopause. Magnetic resonance imaging studies demonstrate that fibroids shrink by up to 40% of their volume in most women through the menopausal transition. A reduction in any pressure symptoms experienced is seen and any heavy menstrual bleeding will cease at the time of menopause. The use of postmenopausal HRT may be associated with an increase in volume of existing fibroids but not with the development of new fibroids. Fibroids are not a contraindication to HRT, provided that the woman is counselled to report any new symptoms and regularly followed up, with ultrasound documentation of the fibroids if clinically indicated.

For women still experiencing heavy menstrual bleeding in the perimenopause, the use of an intrauterine system has been shown to be cost effective, rendering 91% of women amenorrhoeic after one year of use and reducing the need for hysterectomy, while providing progestogenic opposition as part of HRT, if needed, for menopausal symptoms.

Perimenopausal women with symptomatic fibroids can be effectively treated with gonadotrophin-releasing hormone (GnRH) agonists or ulipristal acetate, which induces amenorrhoea more quickly, while waiting for the decrease in fibroid volume seen after menopause. GnRH agonists cause hormonal downregulation, which induces a menopause-like state, leading to fibroid shrinkage and amenorrhoea within three months. They also cause menopausal symptoms and a drop in bone mineral density if used long term, which can be alleviated by the addition of add-back HRT.

Selective progesterone receptor modulators such as ulipristal acetate are a class of drugs licensed for the treatment of fibroids. They reduce the median fibroid volume by over 50%, stopping bleeding within 10 days of use and giving up to 90% amenorrhoea after three twelve-week cycles of treatment. They are licensed for the preoperative treatment of women with large fibroids to facilitate easier myomectomy or hysterectomy and, more recently, have been approved for the long-term management of uterine fibroids.

Endometrial polyps

There are limited data to suggest that postmenopausal HRT may be associated with an increased risk of benign endometrial polyps, especially high-estrogen doses with low potency progestogens. These may present as postmenopausal bleeding or breakthrough bleeding on HRT. Any suspicious bleeding pattern should be appropriately investigated.

Endometriosis

A history of endometriosis can present a difficult management problem, as estrogen treatment can theoretically reactivate the disease, even when the woman has had apparent surgical removal of all the endometriotic tissue. Concerns relate to the potential recurrence of disease and associated symptoms and, rarely, malignant transformation in any residual or reactivated deposits. The risks, however, seem to be small and the data are limited. Women with a history of endometriosis may be at particular risk of the long-term consequences of estrogen deficiency as a consequence of repeated courses of ovarian suppression with gonadotrophin hormone-releasing analogues or bilateral oophorectomy. There is no agreed consensus on the correct HRT combination for these women and much will depend on individual assessment, the severity of the original disease and the extent of any surgical removal. In women with severe endometriosis where there has been extensive or residual disease at the time of surgery, continuous combined estrogen and progestogen replacement or tibolone is favoured by many gynaecologists to minimise the risks of reactivation of residual disease. There is no clear evidence to suggest how long the combined treatment should be continued before reverting to estrogen alone, but its use needs to be balanced against the potential increased risks associated with combined hormone therapy.

Polycystic ovary syndrome

Women with anovulation secondary to polycystic ovary syndrome (PCOS) have chronic estrogen stimulation of the endometrium, with lack of ovulation and deficient progesterone secretion. This may result in an excess risk of endometrial hyperplasia and endometrial carcinoma, although epidemiological evidence for this association is limited. They may also have other risk factors for endometrial cancer, including hyperinsulinaemia and obesity.

After the menopause, women with a history of PCOS continue to have higher serum androgens and metabolic abnormalities, such as impaired

glucose tolerance, higher triglycerides, lower high-density lipoprotein (HDL) when compared with other women, especially when there is a family history of diabetes.

Higher coronary artery calcium scores, which is a marker for cardiovascular disease, have been observed in women with PCOS compared with controls, in addition to impaired endothelial function. The increased prevalence of these risk markers raises concerns that women with PCOS may be at higher risk for type 2 diabetes and coronary heart disease after menopause but evidence of an increased cardiovascular mortality associated with PCOS has not been demonstrated.

If required, there is no reason why women with PCOS cannot have HRT but the above factors should be taken into consideration when choosing an appropriate preparation.

Cardiovascular disease

Cardiovascular disease is the most common cause of death in women in Europe. Although relatively uncommon before the menopause, the incidence increases sharply in the decade after the menopause, and menopausal status is considered an independent risk factor for cardiovascular disease. HRT is not contraindicated in women with established cardiovascular disease or risk factors for it. Many studies have suggested a possible beneficial cardiovascular effect for estrogen replacement started in the 50s or in the early postmenopause (see Chapter 8).

Hypertension

Hypertension is an important health problem with well-established risks. Women should be encouraged to have regular blood pressure checks and any women identified with a persisting clinic blood pressure over 140/90 should have relevant investigations and a cardiovascular risk score undertaken. Treatment should be instigated as recommended in the National Institute for Health and Care Excellence guidelines on the management of hypertension.[1]

There is no evidence from the literature that estradiol-based HRT increases blood pressure or has an adverse effect in women with pre-existing hypertension. HRT can be taken alongside antihypertensive treatment provided that blood pressure remains well controlled. Rarely, conjugated estrogens may cause an idiosyncratic rise in blood pressure, which returns to normal when treatment is stopped. Transdermal estrogen has less effect on the renin–angiotensin system than oral

therapy, so may be a better choice in women at high-risk for hypertension or women in whom hypertension is difficult to control. Data from trials of tibolone and raloxifene do not show an adverse effect on blood pressure.

Valvular heart disease

HRT is not contraindicated in women with valvular heart disease. Women who take anticoagulants may have more problems with irregular or heavy bleeding, particularly with cyclical therapy, which may require an adjustment of the dose of progestogen relative to that of the estrogen.

Hyperlipidaemia

High levels of triglycerides and low-density lipoprotein (LDL) are associated with an increased cardiovascular risk although this can be offset to some extent by increased levels of HDL, a profile which is more commonly seen in premenopausal women. Oral estrogens reduce LDL cholesterol and increases HDL and triglycerides, although there is no evidence that this improvement in the lipid profile is transposed into a drop in cardiovascular risk. This potentially beneficial effect is maintained with the addition of a non-androgenic progestogen or micronised progesterone; however, the addition of an androgenic progestogen, such as levonorgestrel or norethisterone, causes a drop in HDL, somewhat negating the beneficial effect of estrogen on the lipid profile. The transdermal route has less effect on lipids overall and does not increase triglycerides. Thus, HRT needs to be tailored to a woman's lipid profile; for example, in women with hypertriglyceridaemia or diabetes, the transdermal route is preferred to the oral route. For a woman with hyperlipidaemia, an oral estrogen with a non-androgenic progestogen would be preferable. Raloxifene and tamoxifen reduce levels of total cholesterol and LDL while remaining neutral for triglyceride and HDL. However, a large randomised trial (Raloxifene Use for The Heart, RUTH) in women with coronary heart disease or risk factors for the disease, found that raloxifene did not reduce the risk of coronary heart disease.[2]

Statins should be considered as the first choice for lipid-lowering therapy in most women with high cholesterol and a 10-year risk for cardiovascular disease over 10%. HRT is not precluded in women on statins if clinically necessary but their overall cardiovascular risk must be taken into consideration.

Venous thromboembolism

As part of patient assessment, it is essential to ascertain an accurate family and personal history of venous thromboembolism (VTE), as these alert us to the possibility of inherited risk factors for future thrombotic events. Inherited thrombophilias need to be taken into consideration along with acquired risk factors for VTE, such as age, obesity or immobility. Consistent evidence from many studies has shown that oral combined HRT causes an approximately two-fold increase in VTE risk. The Women's Health Initiative study found a hazard ratio of 2.06 (95% confidence interval, CI, 1.6–2.7) with use of combined HRT, greatest in the first year of treatment, and a slightly lower hazard ratio of 1.32 (95% CI 0.99–1.75) with estrogen only. The increased risk appeared immediately on starting treatment and disappeared on cessation.

The presence of an inherited thrombophilias markedly increases the risk of thrombosis. Factor V Leiden, deficiencies in protein S, protein C and antithrombin account for most of these and carry lifetime probabilities of developing thrombosis of up to eight times higher than non-carriers. The presence of factor V Leiden further increases the risk of VTE in women receiving oral HRT compared with placebo (HR 6.7, 95% CI 3.1–14.5). Women with a positive family history of thrombosis are at increased risk of having one of these mutations and thrombophilia testing may be justified in cases where there is a strong family history of VTE, such as multiple first-degree relatives with thrombotic events prior to age 50 years or families having more than one mutation. Criteria for testing are discussed in Chapter 4. A negative thrombophilia screen should not give false reassurance, as there may be other as yet undetected mutations. Women older than 50 years with a personal history of VTE within the previous year, in addition to thrombophilia screening, should be screened for underlying disease, including malignancy and connective tissue disorders.

If a decision to use HRT is made in women with an identified risk, the transdermal route is preferable to oral therapy, as it has less effect on haemostasis and does not appear to increase the risk of VTE. A meta-analysis found no excess risk of VTE in women taking transdermal estrogen (OR 1.2, 95% CI 0.1–1.7), even in those with prothrombotic mutations.[3] With respect to progestogen use, a non-androgenic progestogen or micronised progesterone is preferable, as they are associated with a lower thrombotic risk than other progestogens, such as norethisterone or medroxyprogesterone acetate.

In women at high risk for VTE with intolerable symptoms, it may be necessary to consider anticoagulation to decrease thrombotic risk and

allow HRT to be given. Such scenarios are rare and should be discussed with a haematologist, and the risk of additional bleeding should be considered. Raloxifene and high-dose progestogens also increase the risk of VTE. Tibolone has not been associated with an increased VTE risk, although large-scale studies have not been done and its use is associated with a slightly raised risk of stroke.

HRT and surgery

The NICE guidance on the management of the menopause concluded that there is no need to routinely discontinue transdermal HRT prior to elective surgery, although a discussion with the woman, the surgical and anaesthesia team would be recommended to allow an individualised risk assessment. For those women on oral therapy, there may be a small increased risk that needs to be considered but there is no rationale for routinely stopping HRT prior to all surgery, especially as most of these women would be eligible for routine thromboprophylaxis.

Obesity

Obesity (a body mass index, BMI, over 30 kg/m^2) is increasing dramatically. The 2014 Health Survey for England suggested that around 26.8% of British women are obese, which has huge economic implications for the health services, because of the associated increased risk of multiple health conditions such as cardiovascular disease, VTE, type 2 diabetes, cancer (endometrial, gallbladder, oesophageal adenocarcinoma, renal, breast), osteoarthritis, respiratory problems and gallbladder disease. In 2010, a pooled analysis of 19 prospective studies found that the all-cause mortality is generally lowest within the BMI range of 20.0–24.9 kg/m^2.[4]

The distribution of body fat seems to be important. In the Nurses' Health Study, abdominal obesity was associated with increased risk of hypertension, diabetes, and dyslipidaemia, and raised CVD, cancer and total mortality rates, even in women of normal weight. Hormonal changes at menopause are associated with increases in waist circumference and central abdominal (visceral) fat both in obese and lean women. Conversely, estrogen therapy has a favourable effect on body fat distribution, maintaining the female gynoid shape and preventing the postmenopausal tendency to abdominal obesity, while having a neutral effect on weight.

Obesity is not a contraindication to HRT. However, as obesity increases the risk of VTE, transdermal delivery of estrogen may be preferred.

Endocrine diseases

Diabetes mellitus

The diabetic population is growing, owing the increasing prevalence of obesity and physical inactivity. The Health Survey for England 2014 found that 10.7% of the UK population were at risk of type 2 diabetes, with four million diagnosed diabetics (90% with type 2): a doubling since 1996.

HRT has been shown to decrease the incidence of type 2 diabetes, as well as improving glycaemic control, with results varying according to the type and route of administration. In the Heart and Oestrogen/progestin Replacement Study (HERS) trial, a study into secondary prevention of coronary heart disease, women were followed for the development of type 2 diabetes over four years.[5] The cumulative incidence of type 2 diabetes was 6.2% in the HRT group compared with 9.5% in the placebo group.

The Women's Health Initiative trial reported changes in fasting glucose and insulin during the first year of follow-up, suggesting a decrease in insulin resistance in the hormone group.[6] HRT also improves lipid profiles, with transdermal delivery decreasing triglyceride levels, which may be of particular benefit to diabetics.

Postmenopausal women with diabetes should be considered for HRT for the same indications as other postmenopausal women, incorporating normal strategies for the reduction in cardiovascular disease risk and osteoporosis. Osteoporosis is reported as a potential complication of type 1 diabetes, with a relative risk of hip fracture of 6.9 (95% CI 2.2–21.6) in a Norwegian health survey.[7] In type 2 diabetes, a higher risk of hip fracture is seen than in normoglycaemic women, despite higher bone mineral density.

Women with type 1 or 2 diabetes have an increased risk of endometrial cancer so if given HRT they must receive an adequate dose of progestogen to ensure adequate endometrial protection.

Thyroid disease

Thyroid dysfunction is common in the general population, especially among women, increasing with age but with no clear relationship to the menopause. Thyroid hormones affect the reproductive system through several mechanisms by increasing the synthesis of sex hormone-binding globulin, testosterone and androstenedione, reducing the clearance of estradiol and androgens, and increasing the conversion of androgens to estrone.

Early thyroid failure or subclinical hypothyroidism (elevated thyroid-stimulating hormone, normal thyroxine) was detected in a large UK cohort study in 7.5% of adult women, with annual rates of progression to clinical hypothyroidism of 4.3% in women with anti-thyroid peroxidase antibodies and 2.6% with raised thyroid-stimulating hormone only. Autoimmune hypothyroidism (with positive thyroid peroxidase and/or thyroglobulin antibodies) is eight to nine times more common in women than in men, and tends to become increasingly prevalent with age. Serum thyroid autoantibodies, directed against thyroid peroxidase or thyroglobulin, are detectable in up to 25% of women over age 60 years.

Hypothyroidism is common, affecting 12–20% women over the age of 60 years. If left untreated, patients can develop endothelial dysfunction, decreased cardiac contractility and elevated LDL cholesterol levels. Levothyroxine replacement should be given at a dose of 1.6 μg/kg body weight, reduced in women over 60 years.

Thyroid replacement is not a contraindication to HRT but the dose of thyroxine may need to be increased, as concomitant use of oral estrogens results in liver interactions that raise the concentrations of thyroxine-binding globulin, thus decreasing the levels of free serum thyroxine. This interaction does not occur with transdermal estrogens, so this may be a preferable route in hypothyroid women requiring HRT.

Tamoxifen and raloxifene have estrogen-like effects on the liver and also increase thyroxine-binding globulin levels, leading to decreased serum thyroxine and increased thyroid-stimulating hormone, usually still within the normal range.

Hyperthyroidism is far less prevalent than hypothyroidism, affecting 2–4% women. In postmenopausal women, overt thyrotoxicosis is associated with increased prevalence of atrial fibrillation, and increased bone resorption leading to low bone mineral density and, possibly, fractures. Whether subclinical hyperthyroidism causes low bone mineral density in postmenopausal women is unclear but women who present with hyperthyroidism should be screened for osteoporosis.

Autoimmune thyroid disease is present in 14–27% of women with premature ovarian insufficiency, so these women should be tested for the presence of thyroid peroxidase antibodies and thyroid-stimulating hormone levels measured.

Neurological diseases

Migraine

Migraines are more common in women than men after menarche, with frequency and severity often related to menstruation. Peak migraine prevalence in women occurs in the early 40s, and is also very common in the perimenopausal period, which, like menarche, is characterised by marked fluctuations in estrogen levels. With the lower more consistent levels of estrogen after the menopause, the prevalence of migraine halves, mainly attributable to an improvement in frequency of migraine without aura, a pattern more commonly seen with menstrual migraine; however, the pattern of migraine with aura does not appear to be influenced by the menopause. Women who experience clusters of premenstrual migraines associated with decreasing estrogen levels have shown improvement in symptoms when estradiol is administered transdermally just before the onset of bleeding and left in place for seven days. The initial studies were with 100 µg/24-hour patches but gel and lower doses can be used.

There is no evidence that HRT aggravates migraine but too high an estrogen dose can trigger migraines, which usually resolve as the dose is reduced. As migraine can be triggered by fluctuating concentrations of estrogen, the transdermal route is favoured over the oral route, because it produces more stable plasma levels of estrogen. Sequential progestogen treatment may be a trigger for migraine, so the use of natural progesterones or the levonorgestrel intrauterine system is favoured in women with migraine.

Unlike the contraceptive pill, no data suggest that the risk of ischaemic stroke is increased in women experiencing migraine with aura who take HRT, although the baseline risk of stroke for the latter group would be marginally increased compared with women who do not experience aura. For women with menstrual migraine without aura who need contraception, low-dose combined contraceptive pills in an extended cycle causing prolonged suppression of ovulation can avoid both menses and menstrual migraine. HRT can be taken concurrently with preventive or acute treatments of migraine such as triptans (5-HT1 agonists).

Epilepsy

Data about the menopause, HRT and epilepsy are limited. Severe epilepsy, with frequent seizures, reduces the age of menopause by about three to four years. Seizure frequency may increase in the perimenopause,

and this may be due to fluctuating ovarian steroid levels or sleep deprivation from night sweats. HRT has been shown to increase seizure frequency in postmenopausal women, particularly in those women with menstrual cycle-related epilepsy.

Some anti-epileptic drugs are inducers of liver enzymes but it is not clear whether women who take oral HRT should take an increased dose (as with combined oral contraceptive usage); however, in these women the transdermal route may be preferable to the oral route. Anti-epileptic drugs promote bone loss and increase the risk of osteoporotic fracture. The problem is further compounded by the fact that seizures increase the risk of falls. Data for bone density changes are most robust for enzyme-inducing drugs such as phenytoin, phenobarbital, primidone, carbamazepine and valproate. Less is known about the newer antiepileptic drugs such as topiramate, lamotrigine and levetiracetam.

Recommendations for women taking antiepileptic drugs at risk of osteoporosis include calcium and vitamin D supplementation and weight-bearing exercise on a regular basis. Bone mineral density scans help in identifying women at risk, used together with a FRAX® score, to calculate which women may warrant treatment.

Parkinson's disease

The risk of Parkinson's disease is greater in women with early menopause. Premenopausal unilateral or bilateral oophorectomy also increases the risk of Parkinson's disease, cognitive decline and dementia compared with controls. The risk is linked to age at oophorectomy and is negated by appropriate estrogen replacement. HRT is not contraindicated in Parkinson's and can be used in women taking drugs for Parkinson's disease. However, it is not known whether any particular regimen or route of administration is preferred.

Gastrointestinal conditions

Gallbladder disease

In the UK, about 8% of the population over 40 years has gallstones increasing to more than 20% in people older than 60 years. Randomised trials (HERS and WHI) have shown an increased risk of gallbladder disease with oral HRT.[8,9] The WHI found the excess risk of cholecystitis with oral HRT was calculated to be 9.6 additional cases per 1000 women per five years of combined estrogen–progestin therapy and 14.2 with unopposed estrogen use. The risk of gallbladder disease is less with

transdermal estrogen, although it is not well established whether this route is better in women with pre-existing gallbladder disease.

Liver disease

HRT is contraindicated in women with acute liver disease. In women with a history of liver disease where the liver function tests have failed to return to normal, HRT should only be considered after seeking a liver specialist opinion. The non-oral route of estrogen is advised in women with liver disease to avoid the liver first-pass metabolism, but the evidence is limited.

Inflammatory bowel disease

A major consideration in women with inflammatory bowel disease is the increased risk of osteoporosis, which may result from the disease itself, malabsorption or the long-term use of corticosteroids. The transdermal route of HRT is usually preferred to ensure adequate absorption in disease affecting the small bowel, such as Crohn's disease.

Connective tissue disease

Rheumatoid arthritis

This is a systemic disorder that manifests as a chronic, inflammatory polyarthropathy. Its prevalence increases with age, with women being affected about 2.5 times more frequently than men. Women with rheumatoid arthritis are at increased risk of osteoporosis, as a result of increased bone resorption related to disease severity, steroid use and immobility caused by the disease. There is no evidence to suggest that the use of HRT affects the risk of developing rheumatoid arthritis and it does not induce flares in postmenopausal women. There is some evidence that hormone therapy may influence joint health, with decreased hip and knee joint replacement observed in the Women's Health Initiative study. So there may be advantages for this group in having HRT, which will depend on the woman's symptoms, bone mineral density and risk profile.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a rare multi-system rheumatic disease characterised by fever, arthritis, pericarditis, skin rashes, grand mal seizures, kidney failure or pancytopenia. Autoimmune and

connective tissue diseases such as SLE increase early cardiovascular disease and osteoporosis, either directly or through steroid treatment-associated bone loss. In addition, some of these women may experience premature ovarian failure.

Estrogen increases the susceptibility to SLE through uncertain mechanisms, which may explain the marked female prevalence and the flares seen during pregnancy. Studies of combined oral contraceptive use in patients with SLE found that in women with non-active or mild SLE, combined oral contraceptive use does not appear to increase the risk of disease exacerbation; caution is still advised in prescribing ethinylestradiol, owing to the possibility of an increased risk of disease flare or of thrombosis.

Oral estradiol increases the risk of venous thromboembolic events. Thus estrogen and raloxifene should not be used in women with active disease, a history of venous thrombosis or those with persisting antiphospholipid antibodies who are at increased thrombotic risk. If HRT is indicated, non-oral estrogen administration is recommended because of its neutral effect on coagulation. Complex cases, especially those with high thrombotic risk, should be discussed with a haematologist. The incidence and severity of SLE usually decreases after the menopause, so prolonging exposure to estrogen may not be beneficial.

For osteoporosis prophylaxis, bisphosphonates have been licensed for glucocorticoid-induced osteoporosis and can be used in conjunction with calcium and vitamin D. Several studies of SLE patients treated with immunosuppressive agents have reported an increase in non-Hodgkin's lymphoma and one has shown an increase risk of breast cancer.

Miscellaneous conditions

Respiratory problems

Asthma is a chronic disease of the airways characterised by intermittent reversible airflow obstruction and by a chronic inflammatory airway response with infiltration of eosinophils and lymphocytes. A cyclical worsening of airways obstruction in some female asthmatics can occur during the late luteal phase at a time when circulating progesterone and estrogen levels fall. This premenstrual increase in airways reactiveness is seen mainly in severe asthmatics, as is the reduction of these cyclical changes with combined oral contraceptive use.

Unopposed estrogen appears to be associated with an increased risk of developing asthma, the risk appearing to be greater in non-smokers and women with a history of allergic disease. One prospective study of HRT in pre- and postmenopausal women found a positive dose response

between dose of conjugated estrogens administered and the likelihood of developing asthma. There is less agreement about the risk of asthma associated with combined estrogen and progestogen preparations.

Women with asthma can take HRT if indicated but should be aware that HRT can impact on their control. In women with asthma or chronic obstructive pulmonary disease who have used systemic steroids or high-dose inhaled steroids, bone mineral density needs to be assessed.

Otosclerosis

This condition is inherited as a Mendelian dominant characteristic and leads to progressive deafness. Evidence suggests that pregnancy and combined oral contraceptive use can aggravate this condition. As the natural course of the disease is progressive, it is likely that hearing will become more impaired in women who use HRT in the long term anyway but whether this is related to the HRT or not is not possible to say. Thus, while no specific data has shown that HRT causes deterioration of the disease, caution is advised.

Renal failure

Patients with end-stage renal disease are at increased risk of early menopause, osteoporosis, cognitive dysfunction and cardiovascular disease. There is a paucity of data in this population to define the benefits of estrogen- and non-estrogen-based treatments but, overall, there is no reason why such women should not take HRT if indicated. The transdermal route may be preferable.

Post transplantation

Bone mass is reduced in a high percentage of patients after organ or marrow transplantation, with the prevalence of osteopenia or osteoporosis reported to be as high as 80%. Up to 65% of transplant recipients experience osteoporosis-related fracture, dependent on pre-existing disease and immunosuppressive therapy (owing to a combined effect on ovarian function and a direct toxic effect on bone). Post-transplant glucocorticoid therapy is thought to play a major role in the further reduction in bone mass seen in these patients. The additional role of other immunosuppressant treatments in bone loss is less clear but some evidence suggests that cyclosporine A and tacrolimus produce osteopenia as a result of high bone turnover. Anti-osteoporotic strategies need to be

considered in these women. HRT is not contraindicated and if appropriate should be considered as part of the osteoporosis prevention strategy.

References

1 National Institute for Health and Care Excellence. *Hypertension in Adults: Diagnosis and Management* (Clinical guideline CG127). London: NICE; 2011 (updated 2016).

2 Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al., Raloxifene Use for The Heart (RUTH) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*, 2006; 355(2): 125–37.

3 Olié V, Canonico M, Scarabin PY. Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. *Curr Opin Hematol*, 2010; 17(5): 457–63.

4 Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body mass index and mortality among 1.46 million white adults. *N Engl J Med*, 2010; 363: 2211–19.

5 Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, 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): 1–9.

6 Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, et al., Women's Health Initiative Investigators. 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(7): 1175–87.

7 Forsén L, Meyer HE, Midthjell K, Edna TH. Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trøndelag Health Survey. *Diabetologia*, 1999; 42: 920–5.

8 Cirillo DJ, Wallace RB, Wu L, Yood RA. Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. *Arthritis Rheum*, 2006; 54(10): 3194–204.

9 Simon JA, Hunninghake DB, Agarwal SK, Lin F, Cauley JA, Ireland CC, 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(7): 493–501.

Further reading

Ang WC, Farrell E, Vollenhoven B. Effect of hormone replacement therapies and selective estrogen receptor modulators in postmenopausal women with uterine leiomyomas: a literature review. *Climacteric*, 2001; 4(4): 284–92.

Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, 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(7): 840–5.

Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, et al., Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. *JAMA*, 2004; 292(13): 1573–80.

de Godoy Borges PC, Dias R, Bonassi Machado R, Borges JB, Spadoto Dias D. Transvaginal ultrasonography and hysteroscopy as predictors of endometrial polyps in postmenopause. *Womens Health*, 2015; 11: 29–33.

Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, et al., PEARL II Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med*, 2012; 366(5): 421–32.

European Society of Human Reproduction and Embryology. *Management of Women with Endometriosis Guideline of the European Society of Human Reproduction and Embryology*. Grimbergen, Belgium: ESHRE; 2013.

Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, et al., ELITE Research Group. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med*, 2016; 374(13): 1221–31.

Liu B, Beral V, Balkwill A, Green J, Sweetland S, Reeves G, for the Million Women Study Collaborators. Gallbladder disease and use of transdermal versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. *BMJ*, 2008; 337: a386. doi:10.1136/bmj.a386 .

Lo JC, Feigenbaum SL, Yang J, Pressman AR, Selby JV, Go AS. Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. *J Clin Endocrinol Metab*, 2006; 91(4): 1357–63.

MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study. *Neurology*, 2006; 67(12): 2159–63.

Royal College of Obstetricians and Gynaecologists. *Long-term Consequences of Polycystic Ovary Syndrome* (Green-top Guideline no. 33). London: RCOG; 2014.

Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ*, 2012; 345: e6409. doi: https://doi.org/10.1136/bmj.e6409.