Chapter 47: Menopause and the postmenopausal woman

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Introduction

We live in an era when the population is ageing; at the time of writing more than 30% of women are aged 50 years of age or over. Maintenance of peri- and postmenopausal health is therefore of paramount importance if we are to minimize the economic impact on society in this and future millennia. The recent adverse media on hormone replacement therapy (HRT), still the most effective treatment available for the alleviation of menopausal symptoms, could therefore not have come at a worse time. The controversy surrounding the pros and cons of HRT has left menopausal women, health professionals and society in general, confused as to how best to deal with both the short- and long-term sequelae of the menopause. The immediate symptoms, often debilitating and the long-term sequelae such as osteoporosis, still need to be dealt with, and will take on ever increasing importance because of our ageing society.

Menopause demographics

Two hundred years ago only 30% of women lived through a menopause; now, more than 90% will. Thus, the menopause transition and postmenopause is very much a condition of the 20th and 21st centuries. Life expectancy is now 82 years of age for a woman living in the UK. The majority of women can therefore expect to live over a third of their lives in a menopausal state (Fig. 47.1).

Unfortunately, many of these postmenopausal women will have a progressively declining quality of life. Optimization of menopause health care should produce a rectangularization of society where postmenopausal women remain at the peak of health.

Menopause physiology

The menopause, from the Greek 'Menos' (month) and 'Pausis' (cessation) is defined as the last menstrual period. The diagnosis can only be made retrospectively after

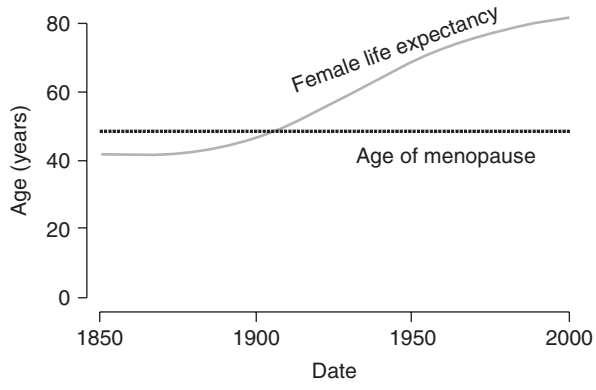

Fig. 47.1 Female life expectancy. From Cole 1976.

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a minimum of 1 year's amenorrhoea. Although the menopause occurs at an average age of 51, the physiological changes which result in the final menstrual period (FMP) can start 10 years prior to this. Hormonal changes continue long after the FMP. This episode of dynamic neuroendocrine change is characterized by 'the climacteric' from the Greek 'Klimax' ladder, i.e. the climb to the menopause. It may be associated with distressing clinical problems such as reduced fertility, menstrual irregularity and vasomotor symptoms. The intermediate sequelae of these changes are typically seen in the skin and urogenital tract and in the long term, in skeletal and cardiovascular pathology.

The declining oocyte pool

A newborn female infant has over a million oocytes; the oocyte cohort shrinks throughout life such that there are only a few thousand oocytes left as a woman enters her forty's and few or none in the postmenopause. It is the depletion of oocytes which eventually leads to the cessation of menstruation, the cardinal sign of the menopause. There are two landmarks in the ovarian failure process. Firstly, there is a marked decline in fertility with no cycle

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dysfunction. Subsequently, cycle changes become noticeable as the follicular phase shortens and luteal phase dysfunction occurs.

Compensated and decompensated failure

Initially, the ovarian failure is compensated by gonadotrophin levels starting to rise, in some women from the age of 30 years. During this time there is evidence for a reduced number of gonadotrophin receptors in perimenopausal ovaries and Inhibin production from granulosa cells falls leading to a reduced Inhibin : FSH ratio. Decompensated failure then occurs due to the critical decline in the oocyte pool leading to further rises in follicle stimulating hormone (FSH) (10 to 20-fold); Luteinizing hormone (LH) rises only 3-fold due to its shorter half-life. Oestrogen levels drop due to a reduction in follicle number and qualitative effect on granulosa cell ageing. There is permanent cessation of progesterone production. Studies have shown that the decline in Inhibin B is progressive and not superior to FSH as a predictor of the FMP [1]. However, the early follicular phase drop is more readily detectable than FSH as an initial predictor of reduced ovarian reserve and menstrual irregularity.

Other hormonal changes

Both adrenal and ovarian androgen levels start to decline, from as early as 20 years of age through to the perimenopause stabilizing by the time of the FMP. Some testosterone continues to be produced by ovarian theca cells. The drop in androgen levels is particularly profound in premature ovarian failure, spontaneous or iatrogenic. Oestrogen therapy can increase sex hormone binding globulin levels which leads to further falls in free androgen levels. The main postmenopausal oestrogen is oestrone which is produced mainly in peripheral adipose tissue and the postmenopausal ovary by aromatization of adrenal androstenedione. The somatotrophic axis becomes less active with ageing leading to insulin resistance and a rise in central adiposity. This in turn leads to the change in body shape from the female gynaecoid shape to the male android shape, itself an independent risk factor for coronary heart disease. There are a number of factors involved in perimenopausal weight gain including genetic predisposition, socio-economic influences, reduction in caloric need and expenditure, reduced lean body mass and a reduction in resting basal metabolic rate.

The menstrual cycle

Anovulatory cycles become progressively common. If three or more menstruations are missed within a 12 month period it is likely that the menopause transition will be completed within 4 years. There can be continued oestrogen production in the absence of progesterone leading to endometrial proliferation, hyperplasia and at its extreme carcinoma. As a result, menstruation can become heavy, prolonged and unpredictable with intermenstrual bleeding (Fig. 47.2).

Prediction of ovarian reserve

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The classic study of the Hutterite population who do not use contraception showed that fertility rates rapidly decrease over the age of 35 years due to reduced oocyte numbers, poor oocyte quality, reduced fertilization and implantation rates, reduced coital frequency and increased chromosomal anomalies. The success of oocyte donation in *in vitro* fertilization (IVF) treatment suggests that the endometrium remains healthy and receptive. Ovarian reserve and response to gonadotrophin stimulation can now be predicted by two methods; firstly, by estimation of early follicular phase FSH levels or Inhibin B and secondly by ultrasonographic measurement of ovarian volume.

An FSH level of >30 is regarded as being diagnostic of the menopause but can be misleading as levels can fluctuate if ovarian activity resumes as often does in the climacteric. Work is currently being conducted to develop an accurate predictive model for the menopause by combining FSH and Inhibin with anti-Mullerian hormone (AMH). There has been a great deal of publicity recently that follicular reserve can be predicted by measurement of ovarian volume [2]. The original work in fact took place over 10 years ago; a nomogram was produced from measurement in over 2,000 normally cycling women where the mean volume was estimated to be 3.57 cm^3 [3]. Further work is required to confirm the predictive value of this model but it is conceivable that a model could be developed which would combine both hormonal and sonographic measurements.

Premature ovarian failure

Premature ovarian failure is said to have occurred when menstruation ceases before the age of 40 years and early menopause before the age of 45 years. Although there are many causes of early ovarian failure, the main cause is spontaneous or idiopathic. The main identified genetic causes are Turner's syndrome and Fragile X. Recently, forkhead genes (FOX03A defect) have been discovered which lead to early follicular activation and thus premature depletion of the follicle pool. Other causes include FSH receptor polymorphisms, where follicles are present but unable to respond due to the loss of the FSH receptor.

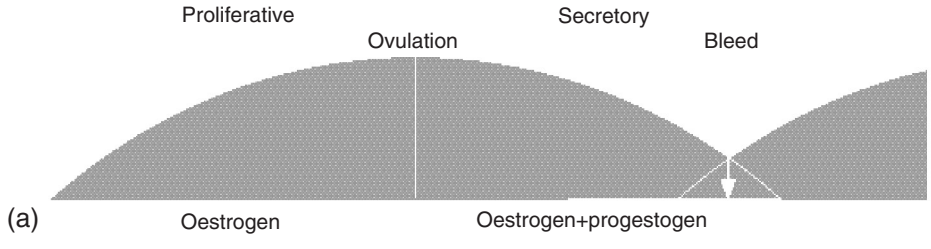

Fig. 47.2 Endometrial effects of perimenopause: (a) Normal cycle; (b) Unopposed oestrogen effect. From Kumar RJ (ed.) (2002) Blaustein's pathology of the female genital tract, 5th edn. New York: Springer.

The proportion of women with iatrogenic premature ovarian failure is growing as increasing numbers of women survive leukaemias, lymphomas and gynaecological cancers due to improved surgical techniques, radiotherapy and chemotherapeutic regimens.

Consequences of the Menopause

Immediate

70% of Caucasians and Afro-Caribbeans suffer from hot flushes and sweats, the commonest menopausal symptoms. This compares to 10–20% of Japanese and Chinese women and may reflect cultural differences or may be diet related (e.g. isoflavone consumption in Asia). Hot flushes are thought to arise due to loss of oestrogenic induced opioid activity in the hypothalamus leading to thermo-dysregulation. It is thought that noradrenaline and serotonin mediate this activity; hence the rationale for using the alpha agonist clonidine and the selective serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine as alternatives to HRT. Obese women are protected from these symptoms due to their production of large amounts of oestrone and their low sex hormone binding globulin levels which leaves more of the free active hormone.

Other typical immediate menopausal symptoms include insomnia, anxiety, irritability, memory loss, tiredness and poor concentration. Mood disturbances can occur due to fluctuation in hormone levels leading to perimenopausal depression. Falling oestrogen levels are thought to lead to similar falls in neurotransmitter levels such as serotonin which trigger these symptoms [4,5]. Women who have suffered from post-natal depression and premenstrual syndrome appear to be particularly predisposed to depression in the perimenopause. Stabilization of hormone levels, e.g. with transedermal oestradiol appears to be particularly effective in ameliorating these symptoms. The effect of menopause on cognitive function is unclear; some studies suggest a reduction in cognitive ability during the menopause transition, e.g. mathematical or visuo-spatial tasks which can be improved with oestrogen replacement but larger randomized studies are required to confirm these findings.

The menopause transition can also be associated with a significant reduction in sexuality and libido. This is not only because of decreased vaginal lubrication leading to dyspareunia but also due to the reduction in androgen levels discussed earlier. In fact, there are more androgen receptors in the female forebrain than in the male which modulate for psychosexual parameters. The drop in androgens is particularly profound in women who have undergone early menopause or premature ovarian failure either spontaneously or due to iatrogenic intervention.

Intermediate

Oestrogen deficiency leads to the rapid loss of collagen which contributes to the generalized atrophy that occurs after the menopause. In the genital tract this is manifested

by dyspareunia and vaginal bleeding from fragile atrophic skin. There is loss of rugations and occasionally stenosis. In the lower urinary tract, atrophy of the urethral epithelium occurs with decreased sensitivity of urethral smooth muscle and decreased amount of collagen in periurethral collagen. All this results in dysuria, urgency and frequency, commonly termed the urethral syndrome. More generalized changes are seen in the older woman as increased bruising and thin translucent skin which is vulnerable to trauma and infection. A similar loss of collagen from ligaments and joints may cause many of the generalized aches and pains so common in postmenopausal women.

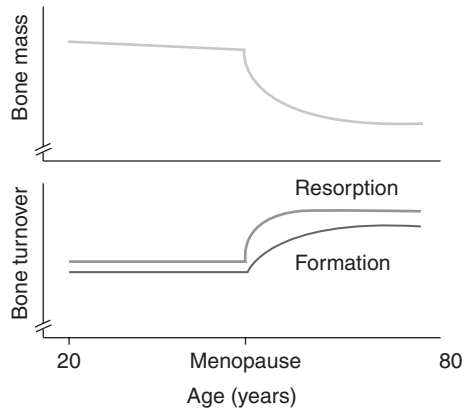

Fig. 47.3 Bone mass and turnover. From [6].

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Long term

Osteoporosis, cardiovascular disease and dementia are three long-term health problems which have been linked to the menopause.

Osteoporosis

Osteoporosis, or osteopenia, is a disorder of the bone matrix resulting in a reduction of bone strength to the extent that there is a significant increased risk of fracture. These fractures cause considerable morbidity in the elderly requiring prolonged hospital care and difficulties in remobilization. The economic consequences are also considerable: in the UK osteoporosis causes more than 150,000 fractures each year with an estimated cost of £1.75 billion per annum in the UK and $5 billion in the USA. With an ageing population and a real increase in the incidence of osteoporosis, this figure will rapidly rise.

Osteoporosis is predominantly a disease of women who achieve a lower peak bone mass than men and are then subjected to an accelerated loss of bone density following the menopause. The hypoestrogenic state leads to activation of the bone remodelling units with an excess of bone resorption relative to formation (Fig. 47.3) [6]. Women lose 50% of their skeleton by the age of 70 years, but men only lose 25% by the age of 90 years. The strength of bone is decreased to such an extent that by 70 years of age, 50% of women will have sustained at least one osteoporotic fracture.

Although the process of bone remodelling or its control has not yet been fully elucidated there is, at present, sufficient information available to conclude that ovarian steroids (oestrogens, androgens, progesterone) play an essential role in skeletal homeostasis. The mechanism of action of sex steroids on the skeleton is still not entirely clear, but it has traditionally included indirect effects on systemic hormones that regulate calcium balance and a direct receptor-mediated action. More recently, changes in cytokine production within the bone marrow, as well as pro-apoptotic and anti-apoptotic effects in the osteoblastic cells, have been proposed as new perspectives on the cellular and molecular mechanisms by which sex steroids influence adult bone homeostasis. Other factors influencing the predisposition to osteoporosis include genetic and racial predisposition, e.g. Afro-Caribbean women are less susceptible to osteoporosis, use of corticosteroids and any factor which predisposes to a hypoestrogenic state including premenopausal amenorrhoea, low weight, smoking and premature ovarian failure. There are several genetic polymorphisms which may predispose to osteoporosis including the vitamin D and oestrogen receptor genes, the collagen 1A1 gene and genes for various cytokines including interleukin 6 and tumour growth factor-β [3].

Cardiovascular

Women are protected against cardiovascular disease before the menopause, after which the incidence rapidly increases reaching a similar frequency to men by the age of 70 years [7]. Surveys of menopausal women have shown that their perceived risk is that 4% will develop heart disease and 46% breast cancer whereas in reality 50% will develop heart disease and 4% breast cancer.

The protective effect of oestrogen in premenopausal women is thought to be mediated by an increase in high density lipoprotein (HDL) and a decrease in low density lipoprotein (LDL), nitric oxide mediated vasodilatation leading to increased myocardial blood flow, an antioxidant effect on endothelial cells and a direct effect on the aorta decreasing atheroma. Cross-sectional and prospective observational studies have shown that women going through the menopause transition have elevation of cholesterol, triglyceride and LDL levels and a reduction in HDL2 levels. A 9-year prospective study of 438 Australian women looked at the risk factors for

women aged 45–55 years having a coronary event. Significant risk factors included a high body mass index (BMI) ($p < 0.001$) and a decrease in oestradiol levels ($p < 0.001$) [8]. A recent study showed that oestrogen status was an independent predictor of atherosclerotic plaque area after controlling for age, hypertension, diabetes, etc [9]. Even normally cycling premenopausal women appear to have an increased cardiovascular disease risk if they have reduced ovarian reserve. Women with a day 3 FSH > 7 IU/l compared to those with a day 3 FSH < 7 IU/l were found to have significantly higher lipid levels, e.g. cholesterol ($p < 0.001$) and LDL ($p < 0.019$) [10].

CNS

Oestrogen also appears to have a direct effect on the vasculature of the central nervous system and promotes neuronal growth and neurotransmission. Studies have demonstrated that oestrogen may improve cerebral perfusion and cognition in women. In the long term this may prevent diseases with a vascular aetiology such as vascular dementia and Alzheimer's as the vasculature is clearly involved in this. In addition to the effect on vasculature in Alzheimer's disease, oestrogen may also intervene at the level of amyloid precursor protein. The failure to show benefit for dementia in older populations, and possibly an increased risk with HRT in some studies (Women's Health Initiative Memory Study [11]), may reflect the predominance of the pro-thrombotic effect of oestrogen in this age group (see 'HRT').

Patient assessment

The diagnosis of the menopause can usually be ascertained from a characteristic history of the vasomotor symptoms of hot flushes and night sweats and prolonged episodes of amenorrhoea. Measurement of plasma hormone levels in patients with classical symptoms are unnecessary, expensive, time consuming and of little clinical significance. However, in the young patient or in a woman after hysterectomy, where the diagnosis is more difficult and the metabolic implications are serious, measurement of FSH levels may be helpful, in which case repeated measurements of 15 IU/L or above may be regarded as climacteric. In patients still menstruating, persistent hot flushes and night sweats are suggestive of the climacteric, but in those patients with psychological symptoms the diagnosis may be more difficult even with an elaborate psychiatric history. In such cases it may be justified to give a trial of oestrogen therapy and monitor the response before discounting a hormonal aetiology.

After the diagnosis has been established, investigations should be no more than the annual screening which is normally applicable to middle-aged women. This should include assessment of weight, blood pressure and routine cervical cytology. Fasting lipid profile estimation may be useful in women with risk factors not only from a general screening point but also if the patient is contemplating starting HRT. A reanalysis of the data from the Women's Health Initiative (WHI) study (see 'HRT controversy') in which women with abnormal baseline lipids were excluded found no excess risk of cardiovascular disease [12]. If abnormal lipids are detected these should be corrected by diet and statins, if appropriate on an individual basis, before HRT is commenced.

Routine breast palpation and pelvic examination is unnecessary; these need only be performed if clinically indicated. Mammography should be performed as part of the national screening programme every three years unless more frequent examinations are clinically indicated. However, if a woman chooses to use HRT beyond the current age of breast screening cessation (65 years), mammographic screening should also continue. In women over 45 years of age it is best to arrange screening before starting oestrogen therapy to identify patients with sub-clinical disease. Endometrial biopsy is not a necessary prerequisite to treatment with HRT unless there are symptoms of postmenopausal bleeding or irregular perimenopausal bleeding. In the few cases where an underlying malignancy is present, bleeding will be irregular after starting treatment, indicating the need for immediate further investigation.

The best currently available measurement of osteoporosis risk is dual energy X-ray absorptiometry (DEXA) measurement of the lumbar spine and hip. Other assessment techniques such as peripheral X-ray screening, e.g. proximal phalanx and calcaneal and ultrasound screening are improving in terms of their sensitivity and correlation with DEXA but the latter still remains the gold standard. Markers of bone formation and breakdown can be useful in that changes occur more rapidly than with bone density but their use is largely confined to research.

There has been some enthusiasm for the implementation of a national osteoporosis screening programme by measurement of bone density, because prediction of osteoporosis from clinical risk factors and the intensity of short-term symptoms is unreliable. This judgement is premature as no studies have yet demonstrated that bone densitometry is suitable for mass screening. The Royal College of Physicians (RCP) has therefore issued guidelines as to which high-risk patients should be targeted for DEXA screening (see 'useful websites'). The RCP advises that DEXA's are performed no more frequently than every 2 years because changes in bone mineral density are so small that they often do not exceed the margin of error of the equipment and assessor.

Therapeutic options

HRT

Oestrogen

Dosage

There is general agreement now that patients should be started on the minimum effective dose of oestradiol and increasing the dose only if needed to alleviate symptoms. Although there is no direct evidence that higher doses of exogenous oestrogen are associated with increased risk of breast cancer or heart disease there is a link with venous thromboembolic risk. Importantly, lower doses of oestrogen are less likely to produce breast tenderness and bleeding problems which will reduce continuance of therapy.

The minimum dosages of currently available systemic oestrogen are as follows:

- 0.3–0.625 mg oral conjugated equine oestrogens
- 1 mg of oral micronized oestradiol or oestradiol valerate
- 25–50 mcg transdermal oestradiol
- 25–50 mg of implanted oestradiol
- 150 mcg transnasal oestradiol
- 50 mcg oestradiol silicone ring

Data suggest that the benefits of a 2 mg dose of oestradiol for symptoms and bone protection can be maintained by a 1 mg dose and similarly the benefits of a 50 mg oestradiol implant are maintained by a 25 mg implant [13]. Studies are currently ongoing to facilitate the licensing of a 0.5 mg oestradiol containing preparation which appears to adequately relieve symptoms. Exceptions to this 'low dose rule' are women who suffer premature ovarian failure who need higher doses of oestrogen to reproduce the physiological hormone levels which would have been present if the ovaries had not failed early. The optimum route of administration or dosage is in this group of young women has yet to be determined.

Route of administration

If we adhere to the principle that we should try to reproduce the most physiological state possible with a 2:1 oestradiol: oestrone ratio then we should avoid the oral route altogether. Oral oestradiol preparations are partially metabolized to oestrone by hepatic first pass metabolism and therefore do not fully restore this ratio. There are twice weekly or once weekly changed transdermal systems containing either oestradiol alone or both oestradiol and progestogen. The combined patches are available in either sequential or continuous regimens. The hormone is adsorbed onto the adhesive matrix which avoids the skin reactions caused by the old alcohol reservoir patches.

Oestradiol can also be used trans-nasally in a 'pulsed' fashion which is thought to maintain the benefits whilst minimizing the side effects of chronically elevated oestrogen, e.g. breast tenderness. It is also available as a low-volume daily transdermal gel or even as a silicone vaginal ring delivering oestradiol systemically for 3 months. The nasal, gel and ring preparations are oestrogen alone and should be combined with progestogen in women with a uterus (see 'Progestogens').

Local (vaginal) oestrogen

Recently developed vaginal HRT regimens have managed to avoid the problem of endometrial stimulation. Creams using oestriol do not produce endometrial hyperplasia and the 17β oestradiol vaginal tablet and silicone vaginal ring also provide effective relief of local symptoms without any significant endometrial effects. These preparations can be used without progestogenic opposition but are only licensed for 3 months use in the UK and 1 year in Europe. Options for local vaginal oestrogen are as follows:

- 0.01% Oestriol cream and pessaries
- 0.1% Oestriol cream
- 25 mcg/24 h Oestradiol vaginal tablets
- 7.5 mcg/24 h Oestradiol releasing silicone ring
- Premarin cream this preparation can potentially cause endometrial hyperplasia and should not be used without progestogenic opposition for more than 3 months

Progestogen/progesterone

Regimens

Oestrogen was originally used unopposed in non-hysterectomized women. It was noted that this led to endometrial hyperplasia in up to 30% of cases. Progestogen has therefore been added to oestrogen therapy for the last 30 years in order to avoid hyperplasia and carcinoma. It is generally accepted that women commencing HRT should start on a sequential regimen, i.e. continuous oestrogen with progestogen for 12 to 14 days per month. The typical dosages of the more commonly used progestogens are shown in Table 47.1.

Bleeding problems

If bleeding is heavy or erratic the dose of progestogen can be doubled or duration increased to 21 days. Persistent bleeding problems beyond 6 months warrant investigation with ultrasound scan and/or endometrial biopsy. After 1 year of therapy women can switch to a continuous combined regimen which aims to give a bleed free HRT regimen which will also minimize the risk of endometrial hyperplasia. Alternatively, women can be switched to the

Table 47.1 Minimum doses of progestogen given orally in HRT as endometrial protection

Progestogen type	Sequential combined daily dosage	Continuous combined daily dosage
C19 – testosterone derived progestogens		
Norethisterone	5 mg	0.5 mg
Levonorgestrel	75 mcg	n/a
Levonorgestrel (IUS)	n/a	20 mcg (10 mcg in development)
Norgestrel	150 mcg	50 mcg
C21- progesterone derived progestogens		
Dydrogesterone	10 mg	5 mg
Cyproterone	2 mg	1 mg
Medroxyprogesterone acetate	5 mg	2.5 mg
Micronized Progesterone	200 mg	100 mg
Cyclogest pessaries	400 mg	200 mg
Crinone gel (4 or 8 %)	Alternate day/12 days of cycle	Twice weekly

IUS, Intrauterine system.

tissue selective agent tibolone. With both these regimens there may be some erratic bleeding to begin with but 90% of those that persist with this regimens will eventually be completely bleed free. If starting HRT de novo a bleed free regimen can be used from the outset if the last menstrual period was over a year ago.

Progestogenic side effects

It is vital that we maximise compliance if patients are to receive the full benefits from hormone replacement therapy (HRT). One of the main factors for reduced compliance is that of progestogen intolerance. Progestogens have a variety of effects apart from the one for which their use was intended, that of secretory transformation of the endometrium. Symptoms of fluid retention are produced by the sodium retaining effect of the renin-aldosterone system which is triggered by stimulation of the mineralocorticoid receptor. Androgenic side effects such as acne and hirsuitism are a problem of the testosterone derived progestogens due to stimulation of the androgen receptors. Mood swings and PMS-like side effects result from stimulation of the central nervous system progesterone receptors [14].

Minimizing progestogen intolerance

The dose can be halved and duration of progestogen can be reduced to 7–10 days. However, this may result in bleeding problems and hyperplasia in a few cases (5–10%) so there should be a low threshold for performing ultrasound scans and endometrial sampling in these women. Natural progesterone has less side effects due to progesterone receptor specificity but is only available in a vaginal form in the UK (200–400 mg pessaries or 4–8% progesterone gel) though micronized oral progesterone is available in France. The levonorgestrel intrauterine system, recently granted a 4 year license in the UK for progestogenic opposition, also minimizes systemic progestogenic side effects by releasing the progestogen directly into the endometrium with low systemic levels. However, in severely progestogen intolerant women, even the low systemic levels of the 20 mcg levonorgestrel intrauterine system can still produce side effects. A smaller, lower dose, 10 mcg system is in phase III clinical trial stage of development and should be ideal for the severely progestogen intolerant woman [15]. A new progestogen, drospirenone, a spironolactone analogue, has recently been incorporated with low dose oestrogen in a continuous combined formulation. It is not only progesterone receptor specific but also has anti-androgenic and anti-mineralocorticoid properties, the former making it useful for hirsuitism and the latter for fluid retention. Also, it may have anti-hypertensive benefits.

Progestogenic risks

The Women's Health Inititiative (WHI) [16] and Million Women Study (MWS) [17] studies showed clearly that there is an excess risk of breast cancer using oestrogen and progestogen HRT compared to oestrogen alone. It has therefore been mooted that even non-hysterectomized women should be treated with oestrogen-only containing preparations. According to the MWS data, after 10 years of oestrogen and progestogen HRT there would be an extra 19 per 1,000 cases of breast cancer and no cases of endometrial cancer; after 10 years of oestrogen alone in non-hystectomized women, there would be an extra 5 cases per 1,000 of breast cancer and 10 cases per 1,000 of endometrial cancer (total 15:1,000). From this simplistic point of view, it would seem reasonable that all women (even with a uterus) should receive oestrogen alone. However, this does not take into account the excess cases of endometrial hyperplasia and bleeding problems. This would generate excessive investigations such as endometrial sampling, hysteroscopies and even hysterectomies which would not be without their own morbidity and mortality.

Current advice remains that progestogenic opposition should still be used. However, it is imperative that we continue to seek improved ways of administering the progestogens which are important in protecting the endometrium in order to avoid progestogenic side

effects and minimize effects on breast tissue, e.g. vaginal and intrauterine progestogens and natural progesterone. However, there is a lack of data as to the risk of breast cancer in women using oestrogen with a levonorgestrel intrauterine system.

Testosterone

Preparations/regimens

Unfortunately, only 100 mg/6 months implanted testosterone pellets are licensed for use in women; 25 mg pellets exist but must be ordered on a named patient basis. The realization that there is currently an unfilled market for female androgen replacement has lead to the development of the 300 mcg per day testosterone transdermal system to treat 'hypo sexual desire disorder'. Whilst the license for this product is awaited it is necessary to continue improvising if one wishes to use preparations other than implants.

One option is to use testosterone gel which comes in 50 mg, 5 ml sachets at a dose of 0.5–1.0 ml/day. If the free androgen index is kept within the physiological range there are rarely any side effects such as hirsuitism. Levels should be checked at baseline and repeated at 4–6 weeks. Research so far has suggested at worst a neutral effect on the cardiovascular system, e.g. arterial compliance and lipid effects. Alternatives to this include scaled down dosages of testosterone injections and oral preparations though many avoid the latter route because of hepatic concerns.

The HRT controversy

Over the last few years, health professionals and their patients have been inundated with information regarding the potential benefits and risks of hormone replacement therapy. Information is available from a variety of sources; some are more reliable than others. The popular press subeditors, responsible for the headlines, often sensationalize the risks of HRT. This has left the average health professional in a very difficult position as to what to advise their patients and has left patients bemused as to where they should turn to obtain reliable advice.

Breast

Recent prospective randomized data from the WHI combined HRT study have confirmed the previous observational data from the Imperial Cancer Research Fund [18] (now 'Cancer Research UK') regarding the risks of breast cancer with HRT. The WHI study was stopped prematurely by the data safety monitoring board after running a mean of 5.2 rather than 8.5 years. This was because it was deemed that the risk versus benefit statistic was exceeded due to an excess of breast cancer and coronary heart disease cases in the treatment arm (continuous combined conjugated equine oestrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg). The data from the WHI study suggested an excess risk of breast cancer with combined hormone therapy of 4 cases per 1,000 women after 5 years. A further analysis of the data this year detected a hazards ratio for breast cancer of 1.24 ($p > 0.001$) for an average of 5.6 year's exposure to HRT [19].

The MWS, a large questionnaire survey by Cancer Research UK of women attending the NHS breast screening programme, reported an increased risk of breast cancer diagnosis with all HRT regimens (Relative Risk [RR] 1.66 95% CI 1.58–1.75); there was a statistically higher risk with oestrogen/progestogen HRT (RR 2.00 [1.91–2.09]) than that seen with oestrogen alone (RR 1.30 [1.22–1.38]) or tibolone (RR 1.45 [1.25–1.67]). This was alarmingly reported by the press as a doubling of risk of breast cancer with HRT, failing to mention the absolute risk in terms of actual numbers of cases. For oestrogen alone it represented an additional 1.5 per 1,000 cases after 5 years of use and for oestrogen/progestogen, an additional 6 per 1,000 cases after 5 years of HRT. In women aged 50–64, whose baseline risk is 32:1,000 anyway, this translated to 33.5 per 1,000 and 38 per 1,000 cases, respectively.

The higher risk estimates from the MWS compared to WHI were probably due to the observational nature of the MWS which underestimated duration of usage of HRT as it did not count years of HRT exposure from baseline to breast cancer reporting on the UK cancer registry. Also, bearing in mind the natural biology of breast cancer development, it is unlikely that the cancers diagnosed after 1 year had developed de novo – it is more likely that these cancers were missed by mammography at baseline and that HRT had acted as a promoter rather than an initiator. Although the MWS reported on there being an increase in mortality, this was of borderline significance RR 1.22 (CI 1.00–1.48) ($p = 0.05$); the absence of tumour details also made it difficult to draw any definitive conclusions on this issue. Numerous authors have expressed their reservations regarding the limitations of both the MWS and WHI data [20,21]. On the positive side, a second WHI study in hysterectomized women using unopposed oestrogen reported that the rate of invasive breast cancer diagnosed was 23% lower in the conjugated oestrogen group compared to the placebo and this comparison narrowly missed statistical significance ($p = 0.06$). This result was unanticipated and appears to suggest that it is the addition of progestogen to oestrogen which leads to the increased risk of breast cancer, not oestrogen alone [22].

Cardiovascular (coronary heart disease and stroke)

Initial cardiovascular data from observational studies suggested up to a 50% reduction in risk of coronary heart disease in HRT users and a neutral effect on stroke. The Heart Estrogen Replacement Study (HERS), however, did not confirm these data in women started on HRT for secondary prevention of coronary heart disease and the WHI did not show any benefit in a primary prevention setting [23]. In fact, WHI suggested that after a mean usage of 5 years there was an excess of heart disease cases in the active treatment arm of the study compared to placebo. The study also found an excess of stroke. The cardiovascular risks in WHI were small, equating to an extra 7–8 cases per 10,000 women per year. These were largely accounted for by an excess of cases in the first couple of years of use, probably due to an initial pro-thrombotic effect of the preparation used. The increase in risk for stroke was clearly age related (age 50–59, 4 cases, 60–69, 9 cases and 70–79 years, 13 cases per 10,000 women per year).

Encouragingly, results from the conjugated oestrogen only arm of the WHI study showed that there was no significant effect on Coronary heart disease (CHD) (primary outcome) compared with placebo (hazard ratio 0.91; 95% CI 0.72–1.15). This latest result again suggests that progestogen may be the problem with HRT. In view of the data from HERS and WHI, guidelines were issued from the American Heart Association and Medicines and Health Care Products Regulatory Agency (MHRA) that HRT should not be used for primary or secondary prevention of CHD.

Future work should now focus on new preparations in younger populations of women. A randomized pilot study from the National Heart and Lung Institute in women using another type of HRT (1 mg oestradiol 0.5 mg norethisterone) after myocardial infarction showed a reduction in risk of re-infarction in the active arm of the study. A larger study, funded by the MRC, is planned as a result of these data [24]. A recent meta-analysis of randomized controlled trials in women using HRT in over 26,000 women showed that in those who started HRT before the age of 60 years there was a 39% lower mortality compared to those on placebo RR 0.61 (CI 0.39–0.95) [25].

Dementia

Observational and case control data suggested a protective effect for oestrogen for the prevention of Alzheimer's disease. These data have not been supported by the recent randomized controlled data from the WHI memory study (WHIMS) which showed that there was a 2-fold increase risk of all-cause dementia [11]. However, the WHIMS data were from an older age group of women (average 67 years) and it may be that the 'window' for Alzheimer's prevention may be in a much younger age group. There is growing evidence that the chief mechanism of action in all types of dementia is infarction secondary to cerebral micro-emboli. This is much more likely to happen if HRT is started in older age group women due to the predominance of pro-thrombotic events in the first few years. In a younger age group, the beneficial physiological effects of oestrogen on blood flow and lipids could potentially lead to long-term benefits [26].

Endometrial cancer

Some authors suggest that sequential combined HRT appears to slightly increase endometrial cancer risk with long-term use [27]. However, continuous combined HRT appears to confer a small protective effect as witnessed by the trend towards protection in the WHI RR 0.83 (0.47–1.47) and other studies [16,28].

The MWS Investigators recently published the analysis of the endometrial cancer data [29]. Non-HRT users had a risk of 3 cases per 1,000 women after 5 years. Encouragingly, sequential combined HRT appeared to have a neutral effect overall on the endometrium. The study confirmed that continuous combined HRT had a protective effect (2/1,000 after 5 years) and that women using oestrogen alone had an increased risk (5/1,000 after 5 years). Surprisingly, there were also a larger number of endometrial cancers reported in the users of the tissue selective agent tibolone (6/1,000 after 5 years). This can possibly be explained by the fact that higher risk women, for example, with a family history of endometrial cancer or with previous bleeding problems, have preferentially been started on tibolone because it has been viewed as a lower-risk product. The results of a large (>3,000 women) prospective randomized trial (THEBES), due to report at the end of 2005, comparing the effect of tibolone to placebo, are eagerly awaited. The safety monitoring board have encouragingly allowed the study to continue unchanged.

Venous thromboembolism

It is clear from studies including HERS and WHI that there is a 2 to 3-fold increase in risk of venous thromboembolism (VTE) with oral HRT with the greatest risk occurring in the first year of use. However, recent data suggest that transdermal therapy may not increase the risk of VTE [30]. There is biological plausibility for this; avoidance of hepatic first pass metabolism minimizes adverse effects on clotting factors and the fibrinolytic system.

Osteoporosis

For many years bone marker and bone density data suggested that HRT had a beneficial effect on the skeleton. The data from the WHI study finally provided strong grade A (randomized placebo controlled) evidence for the gold standard outcome measure, that is, prevention of fractures of the hip and spine (5 less cases per 10,000 women per year).

Colorectal cancer

The WHI study confirmed previous observational studies for the beneficial effect of combined HRT in reducing the incidence of colorectal cancer (6 less cases per 10,000 women per year) although interestingly not with oestrogen alone. As yet, there is still uncertainty as to the mechanism of action of HRT in reducing the risk of colorectal cancer.

Contraindications to HRT

Coronary heart disease, stroke and venous thromboembolism were considered in the previous section.

Natural oestrogens when given to normotensive or hypertensive women do not cause an elevation in blood pressure, and when given in combination with oral progesterone may actually lower blood pressure; therefore, there is no justification for withholding HRT from hypertensive women.

Fibroids are responsive to oestrogens, and involute after the menopause. HRT may continue to stimulate these benign gynaecological tumours causing some to increase in size. This can cause an increase in menstrual blood loss, but in practice this does not usually represent a problem as treatment can easily be discontinued. However, in patients with a good indication who wish to continue therapy, fibroid resection, embolization, myomectomy or hysterectomy are all options available.

Patients who have suffered with endometriosis and become menopausal, are usually 'cured' of their symptoms. Some may wish to consider HRT and recurrence rates of 4% on HRT can be expected. Recurrence of symptoms is alleviated by stopping HRT.

Treatment of patients with a past history of endometrial cancer is controversial, but there are reports of oestrogen use without any detrimental effects in stage I to III disease [31]. Squamous cervical cancer is not oestrogen sensitive. There are no adverse data in ovarian cancer survivors although there may be a very small increased risk of ovarian cancer with long-term unopposed oestrogen use in healthy women. There are no data for adenocarcinoma of the cervix, vaginal or vulval cancer.

Breast cancer must be regarded as the principal contraindication to oestrogen treatment, but high-risk women with a strong family history of breast malignancy or those with benign breast disease should not necessarily be denied treatment. It is unclear what the precise risk of breast cancer recurrence is with HRT use. A study in breast cancer survivors using HRT was terminated because of an apparent excess risk. Unfortunately, this led to the premature termination of two other studies running concomitantly in which no excess risk had been detected [32]. A large tibolone study (LIBERATE) in breast cancer survivors is still in progress and encouragingly has been allowed to continue by the data monitoring board.

Duration of therapy

According to WHI, the risk of breast cancer appears to increase after 4 years. The MWS has shown a significantly increased risk after only 1 year. However, cancers appearing at 1 year must have been present at baseline with HRT acting as a promoter rather than an initiator. An editorial lead in *The Lancet* written by an epidemiologist [33] unrealistically suggested that the duration of therapy should be limited to 3–6 months. Unfortunately, it is recognized that symptoms often return when HRT is ceased, even after many years of use. If the underpinning principle of HRT is that it should be used to improve and maintain a good quality of life, in women in whom this principle is maintained, it is difficult to argue that they should have arbitrary deadlines imposed on them. Thus, duration of therapy requires careful judgement of benefits and risks on an individual basis. If therapy is to be discontinued, the dose should be reduced in a stepwise fashion over a minimum of 6 months to reduce the risk of immediate severe symptom resurgence.

Official prescribing advice

How are health professionals supposed to react to these data and advise their patients? Guidance from the Medicine's and Healthcare Products Regulatory Agency (see 'useful websites') has advised that HRT should not be recommended for primary or secondary prevention of heart disease. It is recommended that HRT be used merely for symptom relief in the short term at the lowest effective dose and alternatives should be considered in the long term for prevention of osteoporosis. Annual reappraisal of HRT use should be carried out with weighing up of the pros and cons on an individual basis. However, the British Menopause Society (see 'useful websites') consensus statement advises that prescribing habits need not be changed by the recent studies because HRT use in the UK

was primarily for symptom relief rather than primary or secondary prevention.

Alternatives to HRT for

Symptoms

There is little scientific evidence that complementary and alternative therapies can help menopausal symptoms or provide the same benefits as conventional therapies. Yet many women use them, believing them to be safer and 'more natural' especially following the current controversies regarding HRT. The choice of treatments is confusing and unlike conventional medicines, little is known about their active ingredients, safety or side effects or how they may interact with other therapies. They can interfere with warfarin, antidepressants and anti-epileptics with potentially fatal consequences. Some herbal preparations may contain oestrogenic compounds and this is of concern for women with hormone dependent disease such as breast cancer. There is also concern about contaminants such as mercury, arsenic, lead and pesticides. Legislation is soon to be introduced which will make it mandatory for herbal preparations to at least be registered with the MHRA. This will at least allow some control over products which may be completely ineffective or dangerous and it is essential that alternatives to licensed preparations should be judged by similar standards.

Why not HRT?

There are a number of reasons why alternatives to HRT may be sought. The main reason is that an individual does not wish to use hormone therapy because they are concerned about the potential side effects and risks. There may be clinician concerns because of the personal or family history of the women, e.g. cardiovascular disease, venous thromboembolism or breast cancer. It may be deemed that an alternative preparation is actually a better choice than traditional HRT. Whilst many more exist (over 200!) focus here is on those preparations for which some trial evidence exists. The increasing use of complementary therapies has been confirmed by recent studies; 68% of women attending a menopause clinic in London had ever tried an alternative treatment for symptoms and that 62% of these women were satisfied with the results [34].

Lifestyle measures

There is some evidence that women who are more active tend to suffer less from the symptoms of the menopause but not all types of activity lead to an improvement in symptoms. High-impact infrequent exercise can actually make symptoms worse; the best activity is aerobic sustained regular exercise [35]. Avoidance or reduction of intake of alcohol and caffeine can reduce the severity and frequency of vasomotor symptoms.

Non-pharmacological alternatives

Gels for vaginal symptoms, e.g. replens

This vaginal bioadhesive moisturizer is a more physiological way of replacing vaginal secretions than with lubricant vaginal gels such as KY jelly. It actually rehydrates the tissues and provides a reasonable alternative to systemic or vaginal HRT.

Pharmacological Alternatives

Progestogens

Progestogens have traditionally been a popular alternative to combined HRT in women with intractable vasomotor symptoms who have contraindications to oestrogen [36]. However, recent studies, e.g. WHI/MWS, have questioned the safety of progestogens because of concerns that the increase in risk of breast cancer with HRT is due to the combination of oestrogen and progestogen (rather than oestrogen alone). Thus, it is probably inappropriate to treat women with progestogens who have an increased risk of breast cancer. The potential risk to the breast also needs to be taken into account when using progestogens as an alternative in those at risk of thromboembolism.

Alpha 2 agonists

Clonidine, a centrally active alpha2 agonist, has been one of the most popular alternative preparations for the treatment of vasomotor symptoms. Unfortunately it is also one of the preparations for which the least evidence exists for efficacy – at best the trial data are contradictory.

Beta blockers

Beta blockers have been postulated as a possible option for treating vasomotor symptoms but the small trials which have been conduced have been disappointing.

Selective serotonin reuptake inhibitors SSRIs/selective noradrenaline reuptake inhibitors SNRIs

A significant amount of evidence exists for the efficacy of SSRIs and SNRIs in the treatment of vasomotor symptoms. Although there are some data for SSRIs such as fluoxetine and paroxetine, the most convincing data are for the

SNRI (venlafaxine) at a dose of 37.5 mg bd [37]. The key effect with these preparations appears to be stimulation of the noradrenergic as opposed to the serotonergic pathways, hence the preferential effect of SNRIs. The trials demonstrate a 50–60% reduction in hot flush frequency and severity. This compares with an 80–90% symptom reduction with traditional hormone therapy. The main drawback with these preparations (especially the SNRIs) is the high incidence of nausea which often leads to withdrawal from therapy before maximum symptom relief efficacy has been achieved. Trials in this area are ongoing.

Gabapentin

Recent work with the antiepileptic drug Gabapentin has shown efficacy for hot flush reduction compared to placebo. Gabapentin at a dose of 900 mg per day has been shown to reduce hot flush frequency by 45% and symptom severity by 54%. Further work is being conducted to confirm the efficacy and safety of this preparation.

Complementary therapies

Amongst the largest group of users of complementary therapies, middle age women, up to 33% of the population have used these preparations at any one time (European Menopause Survey 2005, Organon International website). It is estimated that the cost of complementary therapies amounts to 17 billion US dollars per annum. The majority of the costs are borne by the consumer as these are unlicensed preparations. These preparations are often used by women as they are perceived to be a safe alternative to traditional hormone therapies. However, the safety of a number of these preparations has been called into question. The current regulation of complementary and alternative medicine is inadequate and fragmented with only osteopaths and chiropractors currently regulated professions.

Phytoestrogens

Phytoestrogens are plant substances that have effects similar to those of oestrogens. Since the first discovery of the oestrogenic activity of plant compounds, over 300 plants have been found to have phytoestrogenic activity. Preparations vary from enriched foods such as bread or drinks (soy milk) to more concentrated tablets. The most important groups are called isoflavones and lignans. The major isoflavones are genistein and daidzein. The major lignans are enterolactone and enterodiol. Isoflavones are found in soybeans, chick peas, red clover and probably other legumes (beans and peas). Oilseeds such as flaxseed are rich in lignans, and they are also found in cereal bran, whole cereals, vegetables, legumes and fruit. The role of phytoestrogens has stimulated considerable interest since populations consuming a diet high in isoflavones such as the Japanese appear to have lower rates of menopausal vasomotor symptoms, cardiovascular disease, osteoporosis; breast, colon, endometrial and ovarian cancers. The evidence from randomized placebo-controlled trials in Western populations is conflicting for both soy and derivatives from red clover. Similarly, there are also debates about the effects on lipoproteins, endothelial function and blood pressure. Currently other studies are underway to assess these products.

Soy

Twelve randomized controlled trials have been published comparing various preparations of soy with placebo. Only four out of the nine studies with a treatment phase lasting more than 6 weeks showed a significant improvement in symptoms compared to placebo. The most important of these trials includes a study of 102 women treated for 12 weeks which showed a 45% reduction in hot flushes in comparison to a 30% reduction in the placebo group [38]. Mammographic density, a risk marker for breast cancer, does not appear to be affected by soy preparations even after 2 year usage. However, long-term treatment with soy has raised some concerns with regard to a low risk of endometrial hyperplasia [39].

Red clover

Red clover has a high content of the isoflavones biochanin A and formononetin, while soy contains predominantly genistein, daidzein and glycitein. Soy isoflavones and red clover isoflavones display different affinities for the steroid receptors which may produce differential effects on symptoms though this requires confirmation. Five placebo-controlled studies evaluating the use of red clover isoflavones in the treatment of vasomotor symptoms have been conducted. Whilst the doses of red clover isoflavones (40–160 mg) and the duration of treatment (12–16 weeks) varied in these studies, all showed a numerical reduction in the number of hot flushes compared to placebo [40]. However, the differences only reached statistical significance in two out of the five studies [41]. There were no serious safety concerns associated with short-term administration of red clover isoflavones in any of these studies. Breast density does not appear to be adversely affected by red clover although long-term randomized studies of breast cancer incidence are lacking. Endometrial biopsy data are also lacking though ultrasound scans of endometrial thickness have been reassuring.

Black cohosh

Black cohosh is a herbaceous perennial plant native to North America widely used to alleviate menopausal symptoms. There are four randomized controlled trials using black cohosh but only one of these was placebo controlled. Three trials have shown benefit for vasomotor symptoms including one where black cohosh was compared to conjugated oestrogens but further efficacy data are required [42]. There have been seven serious adverse events reported recently due to hepatotoxicity; one case requiring liver transplantation [43]. There does not appear to be an endometrial effect and there are no clinical trials assessing the effects of black cohosh on the breast.

Evening primrose oil

Evening primrose oil is rich in gamma linolenic acid. Even though widely used by women, there is no evidence for efficacy in the menopause [44].

Dong quai

Dong quai is a perennial plant native to southwest China, commonly used in traditional Chinese medicine. It has not been found to be superior to placebo for menopausal symptoms in one randomized trial. Interaction with warfarin and photosensitization has been reported due to the presence of coumarins.

Ginkgo biloba

Use is widespread but there is little evidence to show that it improves menopausal symptoms. Some studies have shown a benefit for relief of anxiety and depression. There are claims for cognitive benefits from recent studies in postmenopausal women but these require confirmation from large long-term studies [45].

St John's Wort

St John's Wort has been shown to be efficacious in mild to moderate depression both in peri- and premenopausal women due to its SSRI type effect [46], but its efficacy for vasomotor symptoms has not been proven. It has potential interactions with various drugs including warfarin and the pill due to induction of the cytochrome P450 enzymes.

Steroids

DHEA (dehydroepiandrosterone)

Blood levels of DHEA drop dramatically with age. This had led to suggestions that the effects of ageing can be counteracted by DHEA 'replacement therapy'. DHEA is increasingly being used in the USA, where it is classed as a food supplement, for its supposed anti-ageing effects. Some studies have shown benefits on the skeleton, cognition, well-being, libido and the vagina. There is no evidence that DHEA has any effect on hot flushes. The short-term effects of taking DHEA are still controversial and possible harmful effects of long-term use are, as yet, unknown.

Progesterone transdermal creams

Progesterone creams derived from wild yam have been advocated for the treatment of menopausal symptoms and skeletal protection. Claims have been made that steroids (diosgenein) in yams (dioscorea villosa) can be converted in the body to progesterone, but this is biochemically impossible. Progesterone creams have recently been the subject of clinical trials, and no benefit on vasomotor symptoms was demonstrated. Despite previous claims, there was no effect on bone mineral density.

Vitamins and minerals

Vitamins such as E and C, and minerals such as selenium are present in various supplements. The evidence that they are of any benefit to postmenopausal women is lacking.

Homeopathy

Data from case histories, observational studies and a small number of randomized trials are encouraging but clearly more research is needed. A recent paper reported on an investigation of the homeopathic approach to the management of symptoms of oestrogen withdrawal in women with breast cancer. Significant improvements in mean symptom scores were seen over the study period and for the primary end-point 'the effect on daily living' scores. Symptoms other than hot flushes such as fatigue and mood disturbance also appear to be helped [49].

Acupuncture

A recent small randomized controlled trial of 45 postmenopausal women undergoing shallow acupuncture, electro-acupuncture or oral oestrogen administration showed a significant reduction in hot flush frequency in all three groups. The degree of symptom reduction was greatest in the oestrogen group [50]. Although no adverse effects were demonstrated in this study, rare adverse effects such as cardiac tamponade, pneumothorax and hepatitis have been described. Further data are required to establish the precise benefits of acupuncture for the menopause.

Reflexology

Reflexology aims to relieve stress or treat health conditions through the application of pressure to specific points or areas of the feet. While it has been used for various conditions such as pain, anxiety and premenstrual syndrome there have been few studies for menopausal complaints. One randomized trial has been published so far where 67 women with vasomotor symptoms aged 45–60 years were randomized to receive reflexology or non-specific foot massage. There was a reduction in symptoms in both groups but there was no significant difference between the groups [51].

Alternatives to HRT

Skeletal protection

In December 2004, the European Medicines Agency ruled that HRT should no longer be used as a first line treatment for osteoporosis. This advice was mirrored by the MHRA in the UK who proclaimed that the long-term risks of HRT outweighed the benefits and that alternative preparations should be used for osteoporosis prophylaxis and treatment. The National Institute for Clinical Excellence (NICE) has recently carried out a technology appraisal for three of the main alternatives to HRT, bisphosphonates, raloxifene and parathyroid hormone. Treatment guidelines have been issued (Jan 2005 NICE website) but there is a delay in the advice regarding prophylaxis as it was only agreed to issue the latter advice after protests from the National Osteoporosis and British Menopause Societies. The most commonly employed alternatives to HRT for bone protection will now be considered.

Lifestyle measures

Every woman should be encouraged to take plenty of regular exercise in addition to having a well-balanced diet and avoiding smoking. There are studies which show that women who take regular weight-bearing exercise have higher bone mineral densities compared to sedentary controls. Exercise appears to reduce bone loss rather than reverse osteoporosis. It also improves muscle tone thus reducing falls. There is also evidence for reduction in bone loss by the daily use of calcium ($\approx$ 1,500 mg elemental calcium) and vitamin D (4–600 IU) supplements.

Bisphosphonates

Bisphosphonates are pyrophosphate analogues which interfere with osteoclastic resorption. Etidronate was the first bisphosphonate to be licensed but alendronate and risedronate are much more commonly used now due to their significantly higher antiresorptive power. Both these products have grade A randomized controlled trial data for both prevention and treatment of spine and hip fractures (up to 50% reduction), now with 10 year efficacy data for alendronate [52]. There is also good evidence of bone preservation in women who discontinue alendronate though not to the same extent as those who continue therapy. The main side effects of these products are gastro-oesophageal irritation and ulceration although the once weekly preparations have made them more tolerable. In order to improve compliance, a once a month (ibandronate) and a once a year (xolendronate) formulation are in development.

Raloxifene

Raloxifene belongs to the group of compounds called SERMS (Selective Estrogen Receptor Modulators) which are agonistic in the skeleton and cardiovascular system and antagonistic in the breast and endometrium. Raloxifene is the first of these products to be licensed – it produces modest increases in bone mineral density (BMD) (2–3% per annum) and is licensed for fracture reduction in the spine [53]. However, as it lacks grade A evidence for fracture prevention in the hip, NICE have declared it a second line preparation after bisphosphonates (raloxifene).

Strontium ranelate

Strontium ranelate is also antiresorptive and anabolic in its action (dual action bone agent). It has recently been licensed for fracture treatment in both hip and spine (3 year efficacy data with 41% reduction in spine fractures). It has the advantage over bisphosphonates that it does not produce gastrointestinal side effects [54].

Parathyroid hormone (teriparatide)

The parathyroid hormone analogue teriparatide is both antiresorptive and anabolic and is licensed for treatment of spine fractures. Due to its mode of administration (daily injection) and its expense NICE have advised that it should be used as third line treatment in elderly women with previous fractures with the severest osteoporosis.

Statins

There are limited data for an effect of statins on the skeleton but benefits have not been confirmed by randomized trials in human subjects.

Conclusion

We must not underestimate women's desire for a high quality of life in the menopause. Women will continue to demand HRT or a safe, effective alternative for their symptoms. It is, therefore, our duty to strive to provide the best therapy for women to achieve this goal. With every new study there appears to be a change in advice given by the regulatory agencies as to how we should advise our patients, leading to a great deal of confusion.

Best practice should involve the following:

1 Discussion of lifestyle measures, HRT and alternatives should take place from the outset.

2 Management should be individualized taking into account risks and benefits.

3 The main indication for use of HRT should be for symptom relief rather than for prevention of long-term problems.

4 Low-dose HRT should usually be commenced, except in premature ovarian failure, and increased, if necessary, to achieve effective symptom relief.

5 Rigid cut off's in duration of therapy should be avoided with regular reappraisal (at least annual) of the benefits and risks for each individual.

6 Delivery of services should be from a multidisciplinary team if possible with close liaison with allied specialties and experts.

References

1. Landgren B-M *et al*. (2004) Menopause transition: annual changes in serum hormonal patterns over the menstrual cycle in women during a 9 year period prior to menopause. *J Clin Endocrinol Metab* **89**(6), 2763–9.
2. Wallace WH & Kelsey TW (2004) Ovarian reserve and reproductive age may be determined from measurement of ovarian volume by transvaginal sonography. *Hum Reprod* **19**(7), 1612–7.
3. Goswamy RK, Campbell S & Royston JP *et al*. (1988) Ovarian size in postmenopausal women. *BJOG* **95**(8), 795–801.
4. Panay N & Studd JWW (1998) The psychotherapeutic effects of estrogens. *Gynaecol Endocrinol* **12**(5), 353–65.
5. Studd JWW & Panay N (2004) Hormones and depression in women. *Climacteric* **7**(4), 338–46.
6. Bjarnason NH (1998) Postmenopausal bone remodelling and hormone replacement. *Climacteric* **1**(1), 72–9.
7. Tunstall-Pedoe H (1998) Myth and paradox of coronary risk and the menopause. *Lancet* **351**(9113), 1425–7.
8. Guthrie JR (2004) *et al.* (2004) Association between hormonal changes at menopause and the risk of a coronary event: a longitudinal study. *Menopause* **11**(3), 315–22.
9. Christian RC, Harrington S, Edwards WD, Oberg AL & Fitzpatrick LA (2002) Estrogen status correlates with the calcium content of coronary atherosclerotic plaques in women. *J Clin Endocrinol Metab* **87**(3), 1062–7.
10. Chu MC, Rath KM, Huie J & Taylor HS (2003) Elevated basal FSH in normal cycling women is associated with unfavourable lipid levels and increased cardiovascular risk. *Hum Reprod* **18**(8), 1570–3.
11. Shumaker SA, Legault C, Rapp SR *et al*. (2003) 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 study. *J Am Med Assoc* **289**, 2651–62.
12. Jackson G (2003) Royal College of Physicians of Edinburgh Consensus Statement on HRT.
13. Panay N, Versi E & Savvas MA (2000) comparison of 25 mg and 50 mg oestradiol implants in the control of climacteric symptoms following hysterectomy and bilateral salpingo-oophorectomy. *Br J Obstet Gynaecol* **107**(8), 1012–6.
14. Panay N & Studd JWW (1997) Progestogen intolerance and compliance with hormone replacement therapy in menopausal women. *Hum Reprod Update* **3**(2), 159–71.
15. Raudaskoski T, Tapanainen J & Tomas *et al.* (2002) Intrauterine 10 microg and 20 microg levonorgestrel systems in postmenopausal women receiving oral oestrogen replacement therapy: clinical, endometrial and metabolic response. *Br J Obstet Gynaecol* **109**(2), 136–44.
16. Writing Group for the Women's Health Initiative Investigators (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From Women's Health Initiative randomized controlled trial. *J Am Med Assoc* **288**(3), 321–33.
17. Million Women Study Collaborators (2003) Breast cancer and HRT in the Million Women Study. *Lancet* **362**, 419–27.
18. Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* **350**(9084), 1047–59.
19. Chlebowski RT, Hendrix SL, Langer RD *et al*. (2003) Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. The women's health initiative randomised trial. *J Am Med Assoc* **289**, 3243–53.
20. Gambacciani M & Genazzani AR (2003) The study with a million women (and hopefully fewer mistakes). *Gynecol Endocrinol* **17**, 359–62.
21. (2003) Breast Cancer and hormone replacement therapy: the Million Women Study (Letters). *Lancet* **362**, 1328–32.
22. The Women's Health Initiative Steering Committee (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the women's health initiative randomized controlled trial. *J Am Med Assoc* **291**(14), 1701–12.
23. Hulley S, Grady D, Bush T *et al*., Heart and Estrogen/progestin Replacement Study (HERS) Research Group. (1998) Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *J Am Med Assoc* **280**(7), 605–13.
24. Stevenson J (2003) Long term effects of hormone replacement therapy. *Lancet* **361**(9353), 253–4.
25. Salpeter SR, Walsh JM, Greyber E, Ormiston TM & Salpeter EE (2004) Mortality associated with hormone

AQ: Please provide complete details for Ref. [12].

replacement therapy in younger and older women: a meta-analysis. *J Gen Intern Med* **19**(7), 791–804.
26. Kalantaridou *et al.* (2004) Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. *J Clin Endocrinol Metab* **89**(8), 3907–13.
27. Weiderpass E, Adami HO, Baron JA (1999) Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst* **91**, 1131–7.
28. Sturdee DW, Ulrich LG *et al.* (2000) The endometrial response to sequential and continuous combined oestrogen-progestogen replacement therapy. *BJOG* **197**, 1392–400.
29. Million Women Study Collaborators (2005) Endometrial Cancer and hormone-replacement therapy in the Million Women Study. *Lancet* **365**, 1543–51.
30. Scarabin PY, Olger E, Plu-Bureau G (2003) Differential association of oral and transdermal oestrogen replacement therapy with venous thromboembolism risk. *Lancet* **362**, 428–32.
31. Suriano KA, McHale M, McLaren CE, Li KT, Re A & DiSaia PJ (2001) Estrogen replacement therapy in endometrial cancer patients: a matched control study. *Obstet Gynecol* **97**(4), 555–60.
32. von Schoultz E & Rutqvist LE (2005) Menopause hormone therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst* **97**(7), 471–2.
33. Lagro–Janssen T, Rosser W & Van Weel C (2003) Breast cancer and hormone replacement therapy: up to general practice to pick up the pieces. *Lancet* **362**, 414–5.
34. Vashisht A, Domoney CL, Cronje W & Studd JW (2001) Prevalence of and satisfaction with complementary therapies and hormone replacement therapy in a specialist menopause clinic. *Climacteric* **4**(3), 250–6.
35. Lindh-Astrand L, Nedstrand E, Wyon Y & Hammar M (2004) Vasomotor symptoms and quality of life in previously sedentary postmenopausal women randomised to physical activity or estrogen therapy. *Maturitas* **48**, 97–105.
36. Loprinzi CL, Michalak JC, Quella SK *et al.* (1994) Megestrol acetate for the prevention of hot flashes. *N Engl J Med* **331**(6), 347–52.
37. Loprinzi CL, Kugler JW, Sloan JA *et al.* (2000) Venlafaxine in the management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* **356**(9247), 2059–63.
38. Huntley AL & Ernst E (2004) Soy for the treatment of perimenopausal symptoms – a systematic review. *Maturitas* **47**, 1–9.
39. Unfer V, Casini ML, Castabile L, Mignosa M, Gerli S & Di Renzo GC (2004) Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. *Fertil Steril* **82**, 145–8.
40. Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T & Cummings SR (2003) Phytoestrogen Supplements for the Treatment of Hot Flashes: The Isoflavone Clover Extract (ICE) Study. *JAMA* **290**(2), 207–14.
41. Van de Weijer P & Barentsen R (2002) Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. *Maturitas* **42**, 187–93.
42. Huntley A & Ernst E (2003) A systematic review of the safety of black cohosh. *Menopause* **10**(1), 58–64.
43. Medicines and Healthcare products Regulatory Agency. Black cohosh (cimicifuga racemosa) and hepatotoxicity. (2004) The Current Problems in Pharmacovigilence Oct:10th.
44. Chenoy R, Hussain S, O'Brien PM, Moss MY & Morse PF (1994) Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. *Br Med J* **308**(6927), 501–3.
45. Elsabagh S, Hartley DE & File SE (2005) Limited cognitive benefits in Stage +2 postmenopausal women after six weeks of treatment with Gingko biloba. *J Psychopharmacol* **19**(2), 173–81.
46. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W & Melchart D (1996) St John's Wort for depression – an overview and meta-analysis of randomised clinical trials. *Br Med J* **313**(7052), 253–8.
47. Leonetti HB, Longo S & Anasti JN (1999) Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstet Gynecol* **94**(2), 225–8.
48. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ & Guallar E (2005) Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* **142**(1), 37–46.
49. Thomson EA & Reilly D (2003) The homeopathic approach to the treatment of symptoms of oestrogen withdrawal in breast cancer patients. A prospective observational study. *Homeopathy* **92**(3), 131–4.
50. Wyon Y, Wijma K, Nedstrand E & Hammar M (2004) A comparison of acupuncture and oral estradiol treatment of vasomotor symptoms in postmenopausal women. *Climacteric* **7**(2), 153–64.
51. Williamson J, White A, Hart A & Ernst E (2002) Randomised controlled trial of reflexology for menopausal symptoms. *Br J Obstet Gynaecol* **109**(9), 1050–5.
52. Bone HG, Hosking D, Devogelaer JP *et al.* (2004) Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* **350**(12), 1189–99.
53. Delmas PD, Ensrud KE, Adachi *et al.* (2002) Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* **87**(8), 3609–17.
54. Meunier PJ, Roux C & Seeman E *et al.* (2004) The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* **350**(5), 459–68.
55. Purdie DW (2002) What is tibolone – and is it a SPEAR? *Climacteric* **5**(3), 236–9.

Further reading

Badawy SZA (ed.) (1999) *Clinical Management of the Perimenopause*. London: Arnold Press.
Ernst E, Pittler MH, Stevinson C & White AR (2001) *The Desktop Guide to Complementary and Alternative Medicine*. Edinburgh: Mosby.
Panay N, Dutta R, Ryan A & Broadbent M (2004) *Crash Course in Obstetrics & Gynaecology* (Revision textbook). Edinburgh: Mosby.

Rees M & Keith L (2004) *The Year in Postmenopausal Health*. Oxford: Clinical Publishing.
Rees M & Mander A (2004) *Managing the Menopause Without Oestrogen*. London: Royal Society of Medicine Press,
Studd J. (2000) The management of the menopause, 3rd edn. Parthenon Publishing
Zollman C & Vickers A (1999) ABC of complementary medicine. Complementary medicine in conventional practice. *Br Med J* **319**, 901–4.

Useful web sites

www.the-bms.org (the British Menopause Society site)
www.mhra.gov.uk (the medical and Healthcare Products Regulatory Agency)
www.menopausematters.co.uk
www.amarantmenopausetrust.org.uk
www.pms.org.uk (the Premenstrual Syndrome website)
www.nos.org.uk (the National Osteoporosis Society)
www.menopause.org (the North American society)
http://emas.obgyn.net/ European Menopause Society
http://www.emea.eu.int/ European Medicines Agency
www.imsociety.org (the International Menopause Society)
http://nccam.nih.gov/health/alerts/menopause/ National Centre for Complementary and Alternative Medicine. Alternative therapies for managing menopausal symptoms.
www.phytohealth.org (The PHYTOHEALTH Network aims to establish a pan-European network of institutions dealing with safety and health effect of phytoestrogens, identification of optimal sources and processing technologies).
http://dietary-supplements.info.nih.gov The NIH Office of Dietary Supplements
http://dietarysupplements.info.nih.gov/Health_Information/IBIDS.aspx Office of dietary supplements. IBIDS database.
www.whi.org WHI Website
http://www.rcplondon.ac.uk/pubs/wp_osteo_update.htm Royal College of Physicians Guidelines on Osteoporosis
http://medicines.mhra.gov.uk/ourwork/ monitorsafe-qualmed/currentproblems/currentproblems_oct04.pdf Current Problems in Pharmacovigilance Oct 2004: Review of the Evidence regarding Long term Safety of HRT
http://www.organon.com/news/2005_03_08_women_believe_menopausal_symptoms_require_treatment_with_64_percent_experiencing_severe_problems.asp). (European Menopause Survey 2005, Organon International Website)