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Menopause and hormone replacement therapy

A woman born in 1970 can expect to spend one-third of her life post-menopause. The climacteric period can be challenging for both patients and health care providers, with menopausal symptoms and the physical effects of oestrogen deficiency accounting for a significant proportion of primary care consultations. The use of hormone replacement therapy (HRT) remains a controversial topic and misleading information is widespread. Good management of post-reproductive health can have a significant impact on a woman's current and future well-being. This article aims to provide an overview of the physical, psychological and social consequences of menopause, the menopause consultation and the role of HRT in its management.

The GP curriculum and menopause

Clinical example 3.06: Women's health states that GPs should:

- Know that women-specific health matters will account for over 25% of your time as a GP
- Demonstrate an understanding of the importance of risk factors in the diagnosis and management of women's problems
- Understand how the social and biological features of the peri-menopause and menopause period interact and affect health, social well-being and relationships
- Be able to advise on prevention strategies relevant to women

Terminology

The term menopause is derived from the Greek *menos*, meaning month, and *pausos*, meaning ending. Regarded as the permanent cessation of menstruation and fertility, there is a great deal of confusion surrounding the terminology in the field with health professionals and lay people alike (see Box 1).

Facts and figures: Why this is important

The average menopausal age is around 50 years, with one-in-five women entering the menopause below the age of 45 (Ryan et al., 2014). In the UK, there are an estimated 13 000 000 women currently peri- or post-menopausal (Office for National Statistics, 2011). This equates to one-third of the entire female population. As our ageing population continues to grow, menopause can now be considered a mid-life event.

For many, the menopausal transition is relatively problem-free. However, for a significant minority the physical and emotional effects of menopausal symptoms negatively impact their personal and professional lives to a marked degree. One-in-four women say that the menopause adversely affects their quality of life, and of these, 10% still have problematic symptoms after 15 years (Menopause Matters, 2007).

Although menopause is not a disease state in itself, its physical effects do predispose women to an increased

Box 1. Definitions.

- **(Natural) menopause:** The permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognised to have occurred following 12 consecutive months of amenorrhoea, for which there is no obvious pathological or physiological cause. Menopause occurs with the final menstrual period (FMP), but this is only known with certainty 1 year after the event. No adequate biological markers exist
- **Induced menopause:** The cessation of menstruation following surgical removal of the ovaries or iatrogenic ablation of ovarian function (by chemotherapy, radiation or treatment with gonadotrophin releasing hormone (GnRH) analogues). In the absence of surgery, induced menopause may be permanent or temporary
- **Peri-menopause:** Includes the period immediately prior to natural menopause, when the first clinical, endocrinological and biological features of the approaching menopause commence. It ends 1 year after the FMP
- **Pre-menopause:** This term accompanies the entire reproductive period from menarche up until the FMP
- **Post-menopause:** Defines the time from the FMP regardless of whether this was natural or induced (this can only be known retrospectively with the former)
- **Menopausal transition:** The time before the FMP, when variability in the menstrual cycle is usually increased
- **Climacteric:** The phase marking the transition of a woman from the reproductive state to the non-reproductive state. This phase incorporates the peri-menopause
- **Climacteric syndrome:** This period in a woman's life may be associated with symptoms; if this is the case this term applies
- **Premature menopause:** The age of 40 years is used as the arbitrary cut-off point, below which menopause is deemed to be premature. If menopause occurs before the age of 45 years, this is sometimes termed *early menopause*

Adapted from: International Menopause Society. Menopause terminology. www.imsociety.org/menopause_terminology.php.

risk of conditions such as osteoporosis and cardiovascular disease. These risks are heightened in women who undergo an early or premature menopause and it is vital that this is realised by health professionals in order that serious health consequences are avoided (see Box 2).

Box 2. Menopause and health.

Osteoporosis

- Women can lose up to 20% of their bone mass in the 5–7 years post-menopause
- A post-menopausal woman has a 50% chance of sustaining an osteoporotic fracture in her lifetime; once a fragility fracture has occurred, the risk of future fractures at least doubles
- Women aged over 45 years spend more days in hospital due to osteoporosis than diabetes, heart attacks or breast cancer

Weight gain

- Menopause is implicated in abdominal fat gain, which is strongly associated with poorer health outcomes
- Hormone replacement therapy may prevent this abdominal fat gain

Cardiovascular disease

- Coronary heart disease (CHD) is the most common cause of death in women, accounting for 15% of all deaths
- Oestrogen deficiency increases the risk of CHD and stroke in women

Premature/early menopause

- The risk of developing osteoporosis, CHD and stroke roughly doubles in early menopause
- Premature menopause affects cognition, including verbal fluency and visual memory, and may be linked to an increased risk of dementia

Sources: Ryan et al. (2014); British Menopause Society (2010); International Menopause Society (2012); John Hopkins Medicine (2012).

The menopause consultation

Women may present to their GP to discuss the menopause for a variety of reasons and these consultations are becoming increasingly complex. This is a result of the controversies surrounding hormone replacement therapy (HRT), the large number of other medical options available and the widespread use of complementary and alternative therapies.

Assessment

Initially, the woman's menopausal status should be discussed, including the date of the last period and her bleeding pattern prior to that event. This can then be followed with enquiry into the presence of any menopausal symptoms,(see Box 3), risk factors for osteoporosis, thromboembolic and cardiovascular disease, and the patient's personal views on menopause and the therapeutic options available. As always, it is important

Box 3. Menopausal symptoms.

- Vasomotor
  - Hot flushes (up to 80% women affected)
  - Night sweats
- Urogenital (atrophy-related)
  - Vaginal dryness, discharge, pruritus
  - Dyspareunia
  - Prolapse
  - Recurrent urinary tract infections, dysuria, urgency, frequency
  - Voiding difficulties, incontinence
- Sexual dysfunction
  - As a result of the above, or due to androgen deficiency
  - Non-hormonal factors may also play a part
- Psychological (related to hormonal changes +/− other life events)
  - Mood swings
  - Irritability
  - Anxiety
  - Depression
  - Difficulty concentrating, forgetfulness, 'brain fog'
- Other
  - Palpitations
  - Nausea
  - Insomnia
  - Joint aches
  - Headache
  - Fatigue
  - Thinning of the skin, easy bruising, pruritus
  - Parasthesias/'crawling skin' sensation
  - Hair thinning, dryness and growth of unwanted hair

to cover family history (familial breast cancer in particular) and the issue of contraception, if the latter is relevant.

Investigations

Diagnosis of the menopause is usually based on clinical symptoms as there is little value in checking gonadotrophin and ovarian steroid levels unless the diagnosis is in doubt (e.g. premature ovarian insufficiency (POI)). Follicle-stimulating hormone (FSH) and oestradiol levels fluctuate markedly on a daily basis during the perimenopause.

Hormone levels can, however, be relevant in checking the absorption of HRT delivered via a non-oral route. This is particularly important in patients who have had an oophorectomy and especially those who have undergone a premature menopause. In oral oestrogen replacement, as the major circulating metabolite is oestrone, oestradiol levels will not be representative of the true picture. Therefore, decisions regarding treatment should be symptom-led.

Thyroid disorders are occasionally confused with the menopause, so there should be a low threshold for testing thyroid function. This is particularly important when there has been an inadequate response to HRT. Additionally, certain patients will warrant consideration of rare causes of hot flushes such as phaeochromocytoma and carcinoid syndrome (testing catecholamines and 5-hydroxyindolacetic acid, respectively).

Examination

In terms of examination, current guidance recommends recording of the patient's body mass index and blood pressure. If HRT is to be considered, breast and pelvic examination are not routinely necessary unless clinically indicated (in which case they must be done). There is no need for additional mammography or cervical screening in HRT users, but women should be encouraged to participate in the national screening programmes.

Hormone replacement therapy

Since 2002, following the publication of the results of the Million Women Study (MWS) and Women's Health Initiative (WHI), prescriptions for HRT have dramatically dropped. These studies raised serious concerns over the safety of HRT, particularly in the area of cardiovascular disease and breast cancer. Despite the fact that the validity of both these studies has since been called into question – not least because the findings cannot accurately be extrapolated to the vast majority of women actually prescribed HRT in practice – confusion continues to abound.

British Menopause Society recommendations

In 2013, The British Menopause Society (a registered charity and scientific society directed at the medical profession) published their updated recommendations on HRT (Panay, Hamoda, Arya, & Savvas, 2013). They stated that the decision to use HRT should be a fully informed choice involving an opportunity for women to discuss the pros and cons of HRT and complementary therapies with their health care professional, with particular reference given to dietary and lifestyle factors. The regimen and dose should be individualised, with no arbitrary limits placed on the duration of usage, and this should be reviewed annually. It is essential that women who have undergone premature menopause are encouraged to use HRT until at least the age of natural menopause (around 50 years of age).

Potential benefits of HRT

The clinical indications for HRT can be either symptomatic or preventative, the most common being:

- The relief of vasomotor symptoms
- The prevention of osteoporosis
- The relief of symptoms of urogenital atrophy

Vasomotor symptoms

There is good evidence from randomised controlled trials (RCTs) that oestrogen is the most effective treatment for hot flushes. Improvement is usually seen within 4 weeks of starting therapy, with maximal benefit seen at 3 months.

Urogenital symptoms and sexual function

Vaginal dryness and superficial dyspareunia related to vaginal atrophy have been shown to respond favourably to topical oestrogen treatment. Oestrogen therapy may also help relieve symptoms of urinary frequency and urgency as it has a proliferative effect on the urinary epithelium and bladder.

Quality of life

Although not a primary indication to start HRT, short-term treatment may improve mood and depressive symptoms. Reports also suggest that HRT may improve sleep, relieve muscular aches and pains, and enhance overall quality of life.

Osteoporosis and connective tissue

HRT is effective in maintaining bone mineral density and leads to a reduction in osteoporosis of both the hip and spine, as well as reducing the risk of osteoporosis-related fractures. It is the first-line therapeutic intervention for the prevention and treatment of osteoporosis in menopausal women below the age of 50 and those with POI. The bone-protective effect of oestrogen is dose-related, but there are positive effects even with a relatively low dose. Furthermore, observational data suggest that HRT has a protective effect on connective tissue and may even reverse connective tissue loss.

Cardiovascular

Recent data from the Danish Osteoporosis trial have shown that if HRT is commenced within 10 years of the menopause then the incidence of coronary heart disease (CHD) is reduced by 50% (Schierbeck et al., 2012). This is referred to as the 'window of opportunity' for primary prevention.

The 'KEEPS' RCT demonstrated that low-dose HRT commenced in women less than 3 years after their last menstrual period (LMP) had a neutral impact on cardiovascular risk markers.

Cognition

Observational data suggest that women who have undergone an early menopause may see an improvement in cognitive function with HRT, with a possible reduction in the long-term risk of Alzheimer's and all-cause dementia (Lethaby, Hogervorst, Richards, Yesufu, & Yaffe, 2008). However, more research is needed in this area and, based on current evidence, HRT should not be commenced primarily for the prevention of dementia or for improving cognitive function.

Potential risks of HRT

Venous thromboembolism

Current use of oral HRT increases the risk of venous thromboembolism (VTE) two-fold, with the highest risk occurring in the first year of use. This risk is significantly increased in obesity, advanced age and in patients with a personal or family history of VTE or an underlying thrombophilia (see Box 4 for contraindications). There is evidence that transdermal oestrogen confers very minimal VTE risk, whereas certain progestogens may increase the risk.

Box 4. Contraindications to HRT.

- Undiagnosed vaginal bleeding
- Suspected or active breast or endometrial cancer
- Previous local endometrial stromal sarcoma or granulosa cell tumour
- Previous exposure to diethylstilbestrol
- Active or recent VTE or myocardial infarction
- Active liver disease with deranged liver function tests
- Pregnancy
- Porphyria cutanea tarda

Sources: Price (2014) and www.menopausematters.co.uk/contraindications.php.

Stroke

The evidence surrounding HRT use and stroke risk remains conflicting. This is primarily due to the difficulty in interpreting the available data as a result of differing study designs and the failure in many of these to distinguish between ischaemic and haemorrhagic stroke. According to the WHI, the risk appears to be increased in women taking HRT (combined or oestrogen only), but this risk is lower in women under 60 years of age. The Heart and

Estrogen/Progestin Replacement Study found no increased incidence of stroke with HRT (Hulley et al., 1998).

The effects of HRT may be dose-related and, therefore, the lowest effective dose should always be prescribed. Transdermal oestrogen does not appear to increase the risk of stroke.

Coronary heart disease

As stated previously, the timing of the commencement of therapy has a significant impact on HRT's effects on CHD. Route and dose are also important. 'Early harm' may occur when HRT is started in women over the age of 60 with relative overdoses of oral oestrogen. If HRT is to be commenced in women over the age of 60, or those with a previous history of cardiovascular disease, the decision should be a fully informed one and the lowest effective dose used.

Breast cancer

The true effect of HRT on the risk of developing breast cancer remains contentious:

- The WHI demonstrated a small increase in breast cancer risk after 5 years of combined HRT usage; in the oestrogen-only trial a small but significant decrease was seen
- The MWS found an increased risk with all HRT regimens

There is no evidence of an increased breast cancer risk in women under 50 compared with menstruating women of the same age. It can be helpful to put breast cancer risk into perspective by comparing with other known risk factors such as early menarche, nulliparity, late menopause, obesity and increased alcohol intake (more than two or three units daily). See Box 5 for when to refer for specialist advice.

Box 5. When to refer for specialist advice.

- Multiple treatment failure
- Abnormal bleeding
- Confirmed VTE
- Osteoporosis (confirmed or high risk)
- Premature menopause/POI
- Previous or high-risk of hormone-dependent malignancy
- Initiation of androgen therapy

Endometrial cancer

Oestrogen-only therapy increases the risk of endometrial hyperplasia, which can lead to endometrial carcinoma in women with a uterus; the concurrent use of a progestogen significantly reduces this risk. For this reason, oestrogen-only HRT is only prescribed to women who have undergone hysterectomy.

The use of sequential, combined HRT for longer than 5 years may be associated with a small increased risk of developing endometrial cancer, whereas no increased risk appears to apply to continuous combined regimens. Local vaginal oestrogen preparations are not associated with endometrial stimulation.

Ovarian cancer

Uncertainty remains regarding whether HRT increases the risk of ovarian cancer. The WHI was the only RCT that studied the incidence of ovarian cancer in HRT use; no increased risk was demonstrated. However, a recent meta-analysis of 52 epidemiological studies (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2015) suggested women using HRT incur a mildly elevated risk of developing the disease. Nevertheless, the data do not prove causation and the association is weak.

Regimens

In women with a uterus, HRT should comprise an oestrogen combined with a progestogen. The progestogen is paramount in reducing the risk of endometrial hyperplasia and carcinoma that can occur with the use of unopposed oestrogen. In women who have undergone a hysterectomy oestrogen-only therapy is given (although in cases of previous severe endometriosis a progestogen may also be added to prevent recurrence).

Women who use local vaginal oestrogen alone for the symptoms of urogenital atrophy do not require a progestogen for endometrial protection. These low-dose preparations have not been shown to significantly elevate systemic oestrogen levels; using 10 microgram oestradiol pessaries for a year provides the equivalent dose of a single 1.1 mg oral oestradiol tablet.

Women should be prescribed sequential combined HRT if their LMP was less than a year ago, and continuous combined HRT if they have:

- Taken sequential combined HRT for at least 1 year; or
- It has been at least 1 year since their LMP; or
- It has been at least 2 years since their LMP if they had a premature menopause

Women on oestrogen-only therapy will be on a continuous regimen.

The British National Formulary (Joint Formulary Committee, 2014) contains a very useful discussion on HRT and the preparations that are suitable in different women. It is useful to check this and local guidelines before prescribing.

Routes

There are a number of potential routes for delivery for HRT, including:

- Oral preparations
- Gels or creams

- Patches
- Subcutaneous implants
- Vaginal pessaries
- Oestrogen-releasing vaginal ring
- Levonorgestrel-releasing intrauterine system (LNG IUS) for local progestogen administration

Choice of delivery route depends partly on patient preference and partly on consideration of other risk factors. The transdermal and subcutaneous routes avoid the first-pass effect through the liver and do not confer an increased risk of VTE. These routes are also often more suitable for women with a history of gall-bladder or liver disease, migraines, diabetes, malabsorption, those taking enzyme-inducing drugs and those who experience unpleasant side effects such as nausea on oral preparations. If a woman starts HRT after the age of 60 it is advised that a low-dose transdermal route be used.

Tibolone is a selective oestrogen receptor modulator that combines oestrogenic and progestogenic activity with weak androgenic activity. It can be used in women with a uterus who have had no bleeding for over 12 months, without the need for an additional progestogen. It conserves bone mass and may be helpful in reducing vasomotor symptoms and improving mood and libido. However, it should be borne in mind that tibolone is less effective than combined HRT in alleviating menopausal symptoms. There is also an increased risk of stroke, which severely limits its use in women over 60 years of age.

Androgens

If a woman presents with symptoms consistent with lack of testosterone, and there is biological plausibility for androgen deficiency, it would be prudent to consider supplementation. An example would be the patient who presents several months post-hysterectomy with distressing low sexual desire and fatigue. In surgical menopause, testosterone therapy may also benefit those women who suffer with excessively dry skin and hair and those who have not achieved significant relief from urogenital symptoms with oestrogen therapy alone.

Prior to commencing androgen replacement, it is imperative that all other causes of sexual difficulty and fatigue have been excluded. It is also vitally important to ensure that the patient has an adequate oestrogen level in order to respond appropriately to the testosterone therapy. Serum oestradiol, total testosterone and sex-hormone-binding globulin should be measured; the latter enables calculation of the free androgen index. This then allows us to establish the true androgen status – the level of bioavailable testosterone.

Unfortunately, the options for female androgen supplementation are limited. Testosterone patches and implants have recently been withdrawn – for commercial, not safety, reasons – although implants are still available in a few specialist clinics. Testosterone gels, licensed for males, are available and unlicensed prescribing by specialists is an option. As mentioned above, tibolone has a weak androgenic effect and may impact libido and mood positively.

Risks and side effects of androgen therapy are minimal and reversible if levels are maintained within the female physiological range. Data on efficacy and safety continue to accumulate.

Adverse effects of HRT

Oestrogen-related side effects (e.g. breast tenderness, nausea and headaches) may occur continuously or randomly throughout the cycle. Women should be encouraged to persist with treatment for at least 3 months as adverse effects may resolve. Persistent side effects may be improved with a change in route, dose or regimen.

Progestogenic side effects (e.g. fluid retention, acne, pre-menstrual-like syndrome) tend to be cyclical and can be problematic in combined HRT; they are cited often as one of the main reasons for discontinuation of therapy. Halving the dose or reducing the duration of therapy to 7–10 days a month may help, as will consideration of natural progesterone in the form of oral capsules, gels or trans-vaginal pessaries. The LNG IUS may further reduce systemic side effects and provides adequate endometrial protection, being licensed for use in HRT for 4 years.

Monthly cyclical regimens should produce regular predictable bleeding towards, or soon after, the end of the progestogen phase. It is compulsory to investigate unexplained bleeding before changing treatment, to exclude pelvic pathology. On continuous HRT, any bleeding beyond 6 months or after a spell of amenorrhoea requires further investigation or referral.

HRT after cancer

Each year in the UK 15 000 women undergo a bilateral salpingo-oophorectomy as a result of gynaecological cancer (Price, 2014). HRT not only helps moderate the risks and symptoms associated with a surgical menopause, it can also reduce the effects of harsh treatment regimens and improve quality of life. Decisions regarding HRT following gynaecological/hormone-dependent cancer should be individualised and involve the patient, GP, gynaecologists, surgeons and oncologists (see Box 6).

Box 6. HRT after gynaecological and hormone-dependent cancers.

Ovarian cancer

- There is no evidence that oestrogen replacement therapy following ovarian cancer adversely affects prognosis

Cervical cancer

- There are no contraindications to HRT use following treatment for cervical carcinoma; unlike the contraceptive pill, there is no association between HRT use and cervical cancer

Endometrial cancer

- There is no evidence that HRT is contraindicated after successful treatment of endometrial carcinoma
- Low-grade endometrial stromal sarcoma (very rare) is hormone-dependent and is considered a contraindication to HRT

Vulval cancer

- Systemic and topical oestrogen can be used following vulval carcinoma; there is no evidence of an adverse effect with regard to recurrence

Breast cancer

- Conventional advice is to avoid systemic oestrogen-based preparations, especially in women with previous oestrogen receptor-positive tumours. However, most observational studies of patients with breast cancer who have been prescribed systemic HRT have not shown adverse effect on survival. Preliminary analysis of two RCTs in Scandinavia has shown contradictory results
- This group of women continues to pose a management problem, as the menopausal symptoms of iatrogenic breast cancer treatment can be severe
- The view of the International Menopause Society is that women with a past history of breast cancer should not necessarily be excluded from treatment of urogenital symptoms with low-dose vaginal oestrogens

Sources: Panay et al. (2013); Rees, Stevenson, Hope, Rozenberg, and Palacios (2011).

Premature ovarian insufficiency

POI, or premature menopause, has been estimated to affect around 1% of women under 40. However, data from a study carried out at Imperial College London suggest the figures may be much higher, affecting approximately 1-in-20 young women (Islam & Cartwright, 2011).

In women where this diagnosis is suspected, FSH should be measured whether or not they have undergone a hysterectomy. Ideally, the levels should be checked on day 3 to 5 of the menstrual cycle. Where this is not possible (e.g. in a patient who has had a hysterectomy) two samples should be obtained, ideally 2 weeks apart. Of note, FSH is not a reliable indicator of ovarian failure in women using combined hormonal contraception (FSH levels can, however, be accurately measured in those patients on progestogen-only methods).

Importantly, the findings of the WHI study do not apply to this group of patients. For these patients, HRT merely replaces ovarian hormones that would ordinarily be naturally produced. Therefore, these young women are advised to take HRT to control menopausal symptoms and minimise the risk of osteoporosis, cardiovascular disease and, potentially, Alzheimer's disease.

HRT should be continued until at least the age of natural menopause. The contraceptive pill can be used as an alternative to control symptoms, but HRT is generally favoured over the oral contraceptive pill as there is little data on the long-term effects of risk reduction regarding cardiovascular disease and osteoporosis in the latter.

Alternatives to HRT

Some women are unable or unwilling to take HRT and may be keen to consider other medical or complementary options. For the treatment of vasomotor symptoms, selective serotonin and noradrenaline reuptake inhibitors, clonidine and gabapentin may be used. The efficacy of alternative treatments is lower than with HRT, with 50–60% symptom reduction compared with 80–90%.

The National Institute for Health and Clinical Excellence (NICE) Clinical Knowledge Summaries on menopause do 'not recommend the use of herbal or complementary therapies', although they do offer advice if women are using them, and the British Menopause Society has a fact sheet 'Alternative and complementary therapies' on their website. Further more detailed, information can be found in McBride (2015).

As with HRT, the decision to trial alternative therapies should be individualised and made after a fully informed discussion with the patient. Health promotion, including optimisation of lifestyle and diet should be routine in the management of menopause, regardless of the therapeutic intervention.

Key points

- One-in-four menopausal women experience symptoms that adversely affect their quality of life; 10% still have problematic symptoms after 15 years

- The physical effects of menopause predispose women to chronic health conditions such as osteoporosis and cardiovascular disease
- The decision to use HRT should be a fully informed choice, with the dose, route and duration individualised
- Women diagnosed with POI should be encouraged to use HRT until at least the age of natural menopause (around 50 years of age)
- Arbitrary limits should not be placed on the duration of HRT usage, as long as the benefits outweigh the risks
- Previous gynaecological or hormone-dependent cancer does not necessarily preclude treatment with HRT

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AKT question relating to out of area registration

Single Best Answer Question

A 40-year-old woman works in the solicitor's office opposite your surgery. She lives in the next town but wants to register with your practice as she feels that it would be easier to get to GP appointments closer to her work.

Which ONE of the following statements is TRUE? Select ONE option only.

A. The woman cannot register with you as she lives outside your practice area
B. The woman gives up her right to any home visits if she registers as an out of area patient
C. The woman should be told to ask for dual registration with your practice and a practice close to her home
D. The woman can register but should be informed at registration about the arrangements in place for her care should she be too ill to attend your surgery
E. The woman cannot register with you as your practice is not signed up to the out-of-area directed enhanced service

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