Summary

- FSH (follicle stimulating hormone) is **NOT** required to diagnose perimenopause/menopause in women aged over 45 with typical symptoms [1]
- Women experiencing menopause under the age of 40, with menopausal symptoms and absent or infrequent periods, should have the diagnosis confirmed by two blood tests for FSH level taken four to six weeks apart [1]

Learning bite: premature ovarian insufficiency (POI) [1]

Premature ovarian insufficiency affects one in 100 women aged under 40 years.[6, 40] Women under the age of 40 with menopausal symptoms, and absent or infrequent periods, should have the diagnosis of menopause confirmed by two blood tests for FSH level taken four to six weeks apart.

- Hormone replacement in the form of HRT or the combined oral contraceptive (COC) pill should be offered, and continuation recommended at least until the average age of the menopause (51 years), unless there is a contraindication to the use of hormone therapy
- Both hormone replacement therapy (HRT) and the COC provide bone protection, but HRT may have a beneficial effect on blood pressure compared with COC
- HRT should not be relied upon for contraception

Women who have been diagnosed with premature ovarian insufficiency may occasionally have spontaneous return of ovarian activity, and should be referred to a specialist for contraceptive guidance.[8]

Summary

- Offer HRT for menopause related vasomotor symptoms [1, 41]
- Do not offer selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), or clonidine as first line treatment for vasomotor symptoms [1]

Vasomotor symptoms in women with a history of breast cancer or other hormone related cancer

SNRIs and SSRIs for vasomotor symptoms came out badly compared to placebo in a NICE meta analysis because of the high rate of side effects, with patients often stopping treatment early.[2] However, for women with a history of breast cancer or other hormonally sensitive cancers, in whom hormonal treatments should only be considered under specialist supervision, non-hormonal treatments may be a first line option for management of vasomotor symptoms.[11, 12, 41]

The SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen because of the interaction with cytochrome P450. The Medicines and Healthcare products Regulatory Agency (MHRA) highlighted that there may be an increased risk of death in women taking tamoxifen and paroxetine, related to the length of concomitant use. [13] MHRA noted that a more recent study found no evidence for decreased efficacy with co-administration of CYP2D6 inhibitors and tamoxifen, [43] however their advice remained unchanged due to the strong mechanistic model and weight of evidence.

Observational studies show little evidence that use of antidepressants is associated with adverse outcomes in women receiving tamoxifen.[44, 45] Venlafaxine and citalopram are safe to co-prescribe with tamoxifen.

Other non-hormonal medicinal options that show efficacy for vasomotor symptoms in some of the studies reviewed in the NICE guideline include gabapentin and clonidine.[2]

There is no evidence that compounded bio-identical hormones are safer than licensed HRT in patients with a past history of breast cancer.[1]

Urogenital atrophy

Summary

Offer local vaginal oestrogen for women with urogenital atrophy (including those on systemic HRT) for as long as needed to relieve symptoms.[1]

It is well recognised that oestrogen deficiency can cause significant vaginal and bladder problems, yet this problem is hugely under-recognised and undertreated.[14, 15] Symptoms such as vaginal dryness, soreness, dyspareunia, urinary frequency, nocturia, and urgency are extremely common in postmenopausal women.[42] Urogenital symptoms respond well to oestrogens.[42]

The original UK licence for local vaginal oestrogens was time limited (three to six months with re-evaluation of symptom persistence, or maximally two years with estradiol vaginal delivery system). Following evidence that long term use is safe and no routine endometrial monitoring is needed,[16] the licence indications have changed to "indefinite usage" for some preparations (check the BNF or your local prescribing formulary for details). However, in the authors' view, some women are still having the use of local vaginal oestrogens time limited by health professionals who remain unaware of the licence changes.

Local oestrogens are available as pessaries, creams, or rings, and it is important to discuss the best option with each woman based on individual factors.

The NICE menopause guideline recommends you should explain to women with urogenital atrophy that [1]:

- Symptoms often come back when treatment is stopped
- Adverse effects from vaginal oestrogen are very rare
- They should report unscheduled vaginal bleeding to their GP.

Women with vaginal dryness can try moisturisers and lubricants, either alone or in addition to vaginal oestrogen, depending on their preferences and contraindications.[1] These should ideally be concentration and pH balanced to maximise benefits.

Transient mood changes due to hormonal fluctuations are not uncommon in the menopause transition. However, mood changes including anxiety, irritability, and depression may not be due to the menopause alone. General population studies suggest that most women do not experience major changes in mood during the menopause transition.[2, 17] Therefore, pre-existing anxiety and depression should be excluded

Cognitive disturbances such as forgetfulness or difficulty concentrating may be multifactorial. Cross-sectional studies suggest that these symptoms are unlikely to be related to the menopause,[2, 18] yet slee deprivation caused by hot flushes/night sweats may be a causative factor.

Some women who complain of anxiety and feeling low around the time of the menopause will feel much better with HRT, particularly if the mood change is associated with fatigue due to vasomotor symptoms.[2]

The NICE guideline group reviewed the limited evidence available, which showed that low mood can be ameliorated by hormonal replacement therapy (oestrogen alone) and psychological therapies such as CBT but not from the other non-pharmacological treatments reviewed such as herbal treatments.[2]

The NICE menopause guidance recommends that you should [1]:

- Consider HRT to alleviate low mood that arises as a result of the menopause
- Consider CBT to alleviate low mood or anxiety that arises as a result of the menopause.

The full NICE guideline reviewed moderate quality evidence from one RCT with 88 menopausal women comparing cognitive behavioural therapy (CBT) with usual care,[2] which showed that CBT was significantly more effective than usual care to reduce anxiety and low mood at 26 weeks' follow up. There were several RCTs included in the review looking at anxiety and low mood in relation to oestrogen versus no treatment/placebo, and combined HRT versus no treatment/placebo. The quality of the evidence ranged from very low to moderate, with some showing no significant difference and others demonstrating a significant impact on mood.

NICE also stresses the importance of ensuring that menopausal women, and all the healthcare professionals involved in their care, understand there is no clear evidence for SSRIs or SNRIs to ease low mood in menopausal women who have not been diagnosed with depression.

Venous thromboembolism

Summary

Transdermal rather than oral HRT should be considered for women at increased risk of venous thromboembolism (VTE).[1]

- You should inform women about the small increased risk of thromboembolic events (deep vein thrombosis, pulmonary embolism, and stroke) with oral HRT, compared with baseline population risk
- The risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk
- The NICE menopause guideline recommends that you should consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m^2 [1]
- HRT is still contraindicated for women with a past history of unprovoked DVT / PE [23]
- NICE recommends that you should consider referring menopausal women at high risk of VTE, for example those with a strong family history of VTE or a hereditary thrombophilia, to a haematologist for assessment before considering HRT [1]

Breast cancer

Summary

- HRT with oestrogen alone is associated with little or no change in breast cancer risk [1]
- HRT with oestrogen and progestogen can be associated with an increased risk of breast cancer [1]
- Any increase in risk of breast cancer is related to treatment duration, and reduces after stopping HRT.[1] Risk returns to baseline after stopping HRT (usually after more than five years),[2] suggesting HRT acts as a promoter rather than an initiator [46]

Ovarian cancer

Summary

Observational studies suggest that long term use of oestrogen only or combined HRT may be associated with a small increased risk of ovarian cancer, which returns to baseline a few years after stopping treatment.[31]

The most recent meta analysis suggested an additional risk of ovarian cancer with HRT of one extra case per 5000 women per year.[32]

Long term prospective randomised studies are required to confirm causation and the precise risk with newer, lower dose HRT preparations.

Cardiovascular disease

Summary

Reassure women that HRT does not increase the risk of cardiovascular disease (CVD) if started under the age of 60, and that it doesn't increase the risk of dying from CVD.[1]

The NICE menopause guideline highlights that the presence of cardiovascular risk factors is not a contraindication to HRT as long as they are optimally managed.

NICE also states that both healthcare professionals and menopausal women should be reassured that HRT:

- Does not increase cardiovascular disease risk when started in women aged under 60 years
- Does not affect the risk of dying from cardiovascular disease.

Information on absolute rates of CVD (see tables 1 and 2 in the NICE guideline) can be used to explain to women that the baseline risk of coronary heart disease and stroke for women around menopausal age varies between individuals according to the presence or absence of cardiovascular risk factors. Moreover, you can tell women that:

- HRT with oestrogen alone is associated with no (or reduced) risk of coronary heart disease
- HRT with oestrogen and progestogen is associated with little or no increase in the risk of coronary heart disease.

NICE also recommends explaining to women that taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke. However, it is also important to ensure women know that the baseline population risk of stroke in women aged under 60 years is very low.

Recent data from a Finnish Study provides further evidence for the "window of opportunity" theory that the use of HRT in women under the age of 60 is in fact cardioprotective.[48] This is also supported by the 2016 International Menopause Society guideline,[42] which states that in women who are less than 60 years old, recently menopausal, and with no evidence of cardiovascular disease, the initiation of oestrogen only therapy reduces coronary heart disease and all cause mortality.

Diabetes, dementia, and sarcopenia

Diabetes

HRT does not affect the risk of developing diabetes, and is unlikely to affect glucose control in those already diagnosed with diabetes.[1]

Dementia

The likelihood of HRT either reducing or increasing risk of dementia is unknown.[1]

Sarcopenia risk

Muscle mass and strength decrease with age and can affect the risk of falling, and have a detrimental impact on daily living activities . HRT may have a beneficial effect in improving muscle strength and mass, but this is not certain.[1]

Contraception and the menopause

Summary

- NICE states that there is no value in checking FSH or LH (luteinizing hormone) in women on combined oestrogen and progestogen contraception
- The Faculty of Sexual and Reproductive Healthcare (FSRH) currently advise that FSH levels may be used to help diagnose the menopause, but should be restricted to women over the age of 50 years, and to those using progestogen only methods [8]
- Remember that HRT cannot be relied on for contraception: options include COC instead of HRT, intrauterine system (Mirena) with oestrogen replacement,[10] or progestogen only pill (POP) with combined HRT [7]

Faculty of Sexual and Reproductive Healthcare (FSRH) guidance (2010) [8]

This 2010 guidance on contraception in women aged over 40 years pre-dates the NICE menopause guideline, and is due to be reviewed by the FSRH Clinical Effectiveness Unit (CEU). This guideline does offer advice on using FSH testing in women who are amenorrhoeic as a result of using hormonal contraception, and who need advice on when they can safely stop using contraception. The FSRH guideline states FSH testing for this purpose should be restricted to women over the age of 50 who are using progestogen only methods of contraception.

Other key points from the FSRH guideline include:

- Contraception can generally be stopped at the age of 55 years, but you may need to tailor this advice to the individual
- Women who are not using hormonal contraception, but who have regular menstrual bleeding at the age of 55 years, should be advised to continue with some form of contraception
- Women using non-hormonal methods of contraception can be advised to stop contraception after one year of amenorrhoea if aged over 50 years, and after two years of amenorrhoea if aged under 50 years
- Combined hormonal contraception (CHC) use in the perimenopause may help to maintain bone mineral density
- FSH is not a reliable indicator of ovarian failure in women using combined hormones, even if measured during the hormone free interval
- FSH may be used to help diagnose the menopause, but should be restricted to women over the age of 50 years, and to those using progestogen only methods; the FSRH advise in these circumstances if the level is 30 IU/L or more, the FSH should be repeated after six weeks. If the second FSH level is 30 IU/L or more then contraception can be stopped after one year.

Learning bite: contraception in the perimenopause

Remember that HRT cannot be relied on for contraception. In perimenopausal women who are sexually active and require treatment for menopausal symptoms, you could consider the following options [7]:

- Combined hormonal contraception (if under the age of 50 and not contraindicated) instead of HRT
- Intrauterine system (Mirena),[10] plus oestrogen replacement
- Combined HRT plus barrier method or POP.

The FSRH suggests that, in theory, replicating the dose of progestogen found in HRT preparations using progestogen only contraception may provide enough endometrial protection against the effects of oestrogen replacement. However, there is currently no evidence to show that POP, implant, and injectable provide this protection, and only the intrauterine system (Mirena) is licensed for this purpose. [8]

In 2016 the Medicines and Healthcare products Regulatory Agency (MHRA) advised that "levonorgestrel-releasing intrauterine systems should always be prescribed by brand name because products have different indications, durations of use, and introducers." As of September 2016, Mirena is the only produce licensed for four years' use for endometrial protection as part of a hormone replacement therapy regimen.[10]

Duration of treatment with HRT

Summary

Provide evidence based information to your patients about the menopause and treatment options, to help women make informed, individual decisions about how long to continue treatment.[1, 42]

The NICE menopause guideline advises that women who are taking HRT should be reviewed at three months to assess efficacy and tolerability, and then annually thereafter.[1] Treatment should be reviewed for short term menopausal symptoms, and if these do not improve you should then refer to a health professional with expertise in menopause. NICE also highlights that any risk of breast cancer associated with progestogen and oestrogen HRT is related to duration of use, and reduces after stopping HRT.

In the authors' view, regular review of women taking HRT allows you to adjust the dose or change the preparation to tailor the medication to that individual's needs as she ages. For example, cyclical HRT preparations in a pre-/perimenopausal woman can be changed to continuous combined preparations as the woman progresses into the post-menopause. As women age, lower dose formulations are often more appropriate to minimise risks while maintaining benefits.

At each consultation the risks and benefits should be discussed and the data explained, so that the woman understands her individual benefit/risk profile and how it might change over time. This empowers her to make an informed choice about whether to continue or change medication, which can then be documented in her notes.

It is important to support women in making an individual decision on when to stop HRT, rather than recommending arbitrary limits:

- Since we cannot predict how long symptoms will last, there should be no arbitrary time limits for the use of HRT, and it should be tailored individually to the patient. Data from the WHI trial and other studies support safe use for at least five years in healthy women initiating treatment before the age of 60 [19, 42]
- When women do decide to stop HRT for a trial period to see if it is still required for symptom control, either stopping suddenly or gradually makes no difference to whether or not symptoms will return in the long term, but gradually reducing HRT may limit recurrence of symptoms in the short term.[1]