PrescQIPP
Community Interest Company

Menopause

This bulletin focuses on supporting the diagnosis and management of menopause, including in women who have premature ovarian insufficiency.

Recommendations

- Only prescribe hormone replacement therapy (HRT) for the relief of menopause symptoms that adversely affect quality of life. Review regularly to ensure HRT is used for the shortest time at the lowest dose. This is due to the increased risk of breast cancer with all types of HRT, except vaginal oestrogens, and the increased risk of venous thromboembolism with oral HRT compared with transdermal.
- Where HRT is deemed necessary, offer oestrogen and progestogen/progesterone (progestogen/progesterone to protect against the risk of endometrial cancer) to women with a uterus requiring HRT. Women without a uterus should be offered oestrogen alone.
- Offer vaginal oestrogen to women with urogenital atrophy (including those on systemic HRT) and continue for as long as is needed to relieve symptoms. It should also be considered when systemic HRT is contraindicated, after seeking advice from a healthcare professional with expertise in menopause.
- Advise women with vaginal dryness that over-the-counter vaginal moisturisers and lubricants can be used alone or in addition to vaginal oestrogen.
- Breast cancer risk: oral or transdermal HRT should not be offered routinely to women with a history of breast cancer and it should be stopped in women who are diagnosed with breast cancer. If a woman is at moderate or high risk of breast cancer, generally HRT usage should not be used over the age of 50 years. Oestrogen-only HRT should be used where possible for women with a family history of breast cancer, however oestrogen-only HRT (and tibolone) in women with a uterus increases the risk of endometrial cancer so the risks are finely balanced.
- Advise women using combined HRT (oestrogen and progesterone) not to rely on it for contraception. Instead, progestogen-only pills, depot injectables and implants can be used as contraception alongside combined HRT and the Mirena® 52 mg levonorgestrel intrauterine system can be used alongside oestrogen. Do not use combined hormonal contraception in combination with HRT, but it can be used in eligible women under 50 as an alternative to HRT for relief of menopausal symptoms and prevention of loss of bone mineral density.
- Premature ovarian insufficiency: offer a choice of HRT or a combined hormonal contraceptive, unless contraindicated. It is important to continue treatment until at least the age of natural menopause.
- Bilateral salpingo-oophorectomy: offer HRT to women who have no personal history of breast cancer, but have either a BRCA1 or BRCA2 mutation or a family history of breast cancer, if they have had a bilateral salpingo-oophorectomy before their natural menopause. Continue up until the time they would have expected the natural menopause (average 51 to 52 years). Menopausal symptoms occurring when HRT is stopped should be managed in the same way as natural menopause.
- Each treatment for short-term menopausal symptoms should be reviewed at three months to assess efficacy and tolerability and annually thereafter unless there are clinical indications for an earlier review.

Background

Menopause is when a woman stops having periods as she reaches the end of her natural reproductive life. The average age of menopause in the UK is 51, but this varies widely. Premature ovarian insufficiency occurs in 1 in 100 women and is where menopause occurs before the age of 40 years.[1]

Menopausal symptoms are experienced by eight out of ten women and typically last for four years after their last period, but can continue for up to 12 years in about 10% of women. As well as changes in the menstrual cycle, menopausal symptoms include:

- Vasomotor symptoms, such as hot flushes and sweats
- Musculoskeletal symptoms, such as joint and muscle pain
- Effects on mood, such as low mood
- Urogenital symptoms, such as vaginal dryness
- Sexual difficulties, such as low sexual desire.[1]

National guidance

The National Institute for Health and Care Excellence (NICE) published Menopause: diagnosis and management, NICE guideline [NG23] in 2015, which was subsequently updated in 2019. The update replaced the recommendations on breast cancer risk in NICE NG23 with a link to the MHRA's advice on HRT risks and benefits. A full update of NG23 is currently scheduled for August 2023, to focus on managing urogenital atrophy, the long-term benefits and risks of hormone replacement therapy, and cognitive behavioural therapy for managing menopausal symptoms.[1]

Diagnosis

In otherwise healthy women aged over 45 with menopausal symptoms, the following diagnoses can be made without laboratory tests:[1]

- Perimenopause based on vasomotor symptoms and irregular periods
- Menopause in women who have not had a period for at least 12 months and are not using hormonal contraception
- Menopause based on symptoms in women without a uterus

The following laboratory and imaging tests should not be used to diagnose perimenopause or menopause in women aged over 45 years: anti-Müllerian hormone, inhibin A, inhibin B, oestradiol, antral follicle count and ovarian volume.[1]

A serum follicle-stimulating hormone (FSH) test may only be considered to diagnose:

- Menopause in women aged 40 to 45 years with menopausal symptoms, including a change in their menstrual cycle or
- In women aged under 40 years in whom menopause is suspected.[1]

A FSH test should not be used to diagnose menopause in women using combined oestrogen and progestogen contraception or high-dose progestogen.[1]

Treatment

Treatments for menopausal symptoms range from vaginal lubricants, vaginal oestrogen, and hormone replacement therapy (HRT) to non-pharmacological treatments such as cognitive behavioural therapy (CBT).[1]

Managing short-term menopausal symptoms

Please note: the recommendations in this section are not intended for women with premature ovarian insufficiency (see page 9).

Treatments should be adapted as needed, based on changing symptoms.[1]

Vasomotor symptoms

Women may be offered HRT for vasomotor symptoms if still required, after discussing with them the short-term (up to five years) and longer-term benefits and risks.[1]

Oestrogen and progestogen can be offered to women with a uterus and oestrogen alone to women without a uterus.[1]

Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine should not routinely be offered as first-line treatment for vasomotor symptoms alone.[1]

Psychological symptoms

HRT and/or CBT can be considered to alleviate low mood that arises as a result of the menopause.[1]

It should be explained that there is no clear evidence for SSRIs or SNRIs to ease low mood in menopausal women who have not been diagnosed with depression.[1]

Altered sexual function

NICE recommends the consideration of testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.[1] However, testosterone is not currently licensed in the UK for use in women and therefore this would be an 'off-label' or unlicensed use of a licensed medicine.[1,2]

The response to testosterone with regards to efficacy and adverse effects is highly variable and this is most likely due to varying absorption, metabolism and sensitivity to testosterone. Not uncommonly, adverse effects occur because healthcare professionals and their patients are confused about the appropriate preparation and dose which should be used in women, due to the lack of specific female preparations and information sheets.[3]

Testosterone treatment should only be with formulations that achieve blood concentrations of testosterone that approximate what is normal for premenopausal women.[4] Therefore, male formulations can be used judiciously in small doses with blood testosterone concentrations monitored regularly.[4] Treatment should be trialled for an initial three to six months to assess tolerability and efficacy (discontinuing treatment if it is not effective after six months) and then annually, weighing the pros and cons of treatment.[3]

It is important to note that larger studies are needed to inform clinical recommendations regarding the use of testosterone for hypoactive sexual desire dysfunction in premenopausal women.[4] Furthermore, studies must be undertaken to establish the longer-term cardiometabolic and breast safety of testosterone therapy for women, as this is currently unknown.[4]

Further information on appropriate starting doses, adverse effects, cautions and contraindications can be found at: https://thebms.org.uk/publications/tools-for-clinicians/testosterone-replacement-in-menopause/

Urogenital Atrophy

Vaginal oestrogen may be offered to women with urogenital atrophy (including those on systemic HRT) and treatment continued for as long as needed to relieve symptoms.[1]

Vaginal oestrogen may also be considered for women with urogenital atrophy in whom systemic HRT is contraindicated, after seeking advice from a healthcare professional with expertise in menopause.[1]

If vaginal oestrogen does not relieve symptoms of urogenital atrophy, consider increasing the dose after seeking advice from a healthcare professional with expertise in menopause.[1]

The following information should be explained to women with urogenital atrophy:[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

Routine monitoring of endometrial thickness should not be offered during treatment for urogenital atrophy.[1]

Women with vaginal dryness should be advised that moisturisers and lubricants can be used alone or in addition to vaginal oestrogen.[1] These can be purchased over the counter (OTC) at supermarkets and pharmacies.

The Medicines and Healthcare products Regulatory Agency (MHRA) has launched a public consultation to make Gina 10 microgram vaginal tablets (low dose vaginal estradiol) available for self care from a community pharmacy. The OTC indication is for the treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women aged 50 years and above, who have not had a period for at least year. The consultation ended on 23 February 2022 and more details can be found here.[5]

Starting and stopping HRT

Systemic HRT is available as oral or transdermal preparations. Continuous oestrogen is suitable for women without a uterus.[6] For women with an intact uterus, progestogen is added to oestrogen for the prevention of adverse endometrial effects such as hyperplasia and cancer.[7] Progesterone needs to be taken for at least ten days per 28-day cycle to reduce the additional risk of endometrial cancer. This additional risk is eliminated if a progestogen is given continuously.[8]

- Women without a uterus: Oestrogen alone
- Women with a uterus: Oestrogen and progestogen

Progestogen can be added on a cyclical (sequential) or continuous basis. Or women can take a single preparation which provides both oestrogenic and progestogenic activity.[8]

- Sequential HRT – Oestrogen is taken or applied daily. The progesterone is given for the last 12 to 14 days of each cycle in a monthly cyclical regimen. In a three-monthly cyclical regimen, progestogen is given for 14 days every 13 weeks. The progestogen component may be given in a variety of ways depending on how the oestrogen is being taken e.g. combined with oestrogen in a single tablet or patch, or separately as an oral tablet if the oestrogen is being applied transdermally.[6,8]
- Continuous combined HRT – Oestrogen and progestogen are both taken or applied daily. The progestogen component may be given combined in a tablet or patch with oestrogen, or separately as an oral tablet or the levonorgestrel-releasing intrauterine system (IUS, e.g. Mirena®) if the oestrogen is being applied transdermally.[6,8]
- Single preparation with oestrogenic and progestogenic activity, e.g. tibolone, is taken daily.[8]

A continuous combined regimen may be preferred in postmenopausal women as it does not produce withdrawal bleeding.[6] HRT should only be prescribed for relief of menopause symptoms that adversely affect the quality of life, and reviewed regularly to ensure HRT is used for the shortest time at the lowest dose.[7]

Women with a uterus should understand that unscheduled vaginal bleeding is a common side effect of HRT within the first three months of treatment and should be reported at the three month review appointment. If bleeding occurs after the first three months, this should be reported promptly as this may indicate endometrial cancer and requires further investigation.[1,9]

Women who are stopping HRT should be offered a choice of gradually reducing or immediately stopping treatment.[1] It should be explained that gradually reducing HRT may limit recurrence of symptoms in the short term but gradually reducing or immediately stopping HRT makes no difference to their symptoms in the longer term.[1]

Long-term risks and benefits of HRT

Venous thromboembolism (VTE)

The risk of venous thromboembolism is increased by oral HRT compared with baseline population risk.[1] This risk is greater for oral than transdermal preparations and this should be explained to women when deciding on treatment options.[1]

Menopausal women at high risk of VTE (for example, those with a strong family history of VTE or a hereditary thrombophilia) should be considered for referral to a haematologist for assessment before considering HRT.[1]

Transdermal rather than oral HRT should be considered, if indicated, for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m^2.[1]

Type 2 diabetes

Taking HRT (either orally or transdermally) is not associated with an increased risk of developing type 2 diabetes. For women with type 2 diabetes, HRT is not generally associated with an adverse effect on blood glucose control.[1] Consequently, HRT can be considered for menopausal symptoms, if needed, in women with type 2 diabetes after taking comorbidities into account and seeking specialist advice if needed.[1]

Breast cancer

Explain to women that the baseline risk of breast cancer for women around menopausal age varies from one woman to another according to the presence of underlying risk factors.[1]

However, the risk of breast cancer is increased during use of all types of HRT, except vaginal oestrogens. Some excess risk of breast cancer persists for longer than previously thought after stopping HRT and everyone using HRT or considering HRT should receive information on the risks of breast cancer.[7]

Consequently, HRT should only be prescribed to relieve post-menopausal symptoms that are adversely affecting quality of life.[7]

In addition, people using HRT should be regularly reviewed to ensure it is used for the shortest time and at the lowest dose.[7]

The relative risk of breast cancer in women taking HRT is higher for combined oestrogen-progestogen HRT than for oestrogen-only HRT when compared with women who have never used HRT. The risks of breast cancer for women who use oestrogen combined with progestogen for part of each month (sequential HRT) are slightly lower than with oestrogen plus daily progestogen (continuous HRT). However, the risks are unaffected by the type of oestrogen or progestogen/progesterone, or the route by which HRT is administered (oral or transdermal routes).[7]

Where HRT is necessary, using it for as short a time as possible will help reduce the overall risk. In addition, low-dose vaginal oestrogens do not appear to increase breast cancer risk for women in whom this is a therapeutic option.[7]

HRT (including oestrogen/progestogen combination) should not be offered routinely to women with menopausal symptoms and a history of breast cancer. Only in exceptional circumstances, if menopausal symptoms are severe and the associated risks have been discussed, may HRT be offered.[10] However, HRT is contraindicated in women with a history of breast cancer and so this would be an unlicensed or 'off-label' use.[2,10]

Menopausal women with, or at high risk of, breast cancer should also be offered referral to a healthcare professional with expertise in menopause.[1]

Selective serotonin reuptake inhibitor (SSRI) antidepressants can be considered for women with breast cancer for relieving menopausal symptoms, particularly hot flushes[10] but this is an unlicensed or 'off-label' use.[2,10] However, the SSRIs paroxetine and fluoxetine should not be offered to women taking tamoxifen due to the potential drug interaction[1,10] and preference should instead be given to SSRIs with weak inhibitory effects on CYP2D6, such as citalopram, escitalopram or sertraline.[11]

Women with a family history of breast cancer who are considering taking, or already taking HRT, should be informed of the increase in breast cancer risk. Where possible, oestrogen-only HRT should be prescribed if indicated.[12] However, oestrogen-only HRT (and tibolone) in women with a uterus increases the risk of endometrial cancer so the risks are finely balanced.[13] Generally HRT usage should be confined to women younger than age 50 years if at moderate or high risk of breast cancer.[12]

When women with no personal history of breast cancer have either a BRCA1 or BRCA2 mutation, or a family history of breast cancer, and they have had a bilateral salpingo-oophorectomy before their natural menopause, they should be offered combined HRT if they have a uterus, and oestrogen-only HRT if they don't have a uterus, up until the time they would have expected natural menopause (average age for natural menopause is 51 to 52 years). Menopausal symptoms occurring when HRT is stopped should be managed in the same way as symptoms of natural menopause.[12]

Systemic HRT should be stopped in women who are diagnosed with breast cancer.[10]

Cardiovascular risk

The baseline risk of coronary heart disease (CHD) and stroke for women around menopausal age varies from one woman to another according to the presence of cardiovascular risk factors.[1] The presence of cardiovascular risk factors is not a contraindication to HRT as long as they are optimally managed,[1] however, healthcare professionals should assess carefully every woman's risk of CHD before prescribing HRT, irrespective of her age or time since menopause.[14]

Randomised controlled trials have found an increased risk of CHD in women who started combined oestrogen-progestogen therapy more than ten years after menopause. Very few randomised controlled trials have assessed younger, newly menopausal women, and some have suggested a lower relative risk in these women compared with older women. The low baseline risk of CHD in most younger women, and the very low attributable risk due to HRT, means that their overall CHD risk is likely to be low. No increased risk of CHD with use of oestrogen-only HRT has been identified to date.[14]

It should be explained that taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke however, the baseline population risk of stroke in women aged under 60 years is very low.[1] In randomised controlled trials, oestrogen-only and combined HRT increased the risk of stroke (mostly ischaemic) compared with placebo. Although the increase in relative risk seems to be similar irrespective of age, baseline risk of stroke increases with age and therefore older women have a greater absolute risk.[14]

Endometrial cancer

In women with a uterus, use of oestrogen-only HRT substantially increases the risk of endometrial hyperplasia and carcinoma in a way that depends on dose and duration. Addition of progestogen cyclically for at least ten days per 28-day cycle greatly reduces the risk, and addition of progestogen every day eliminates the risk.[14]

Ovarian cancer

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.[14]

Osteoporosis

Women should be given advice on bone health and discuss these issues at review appointments.[1]

It should be explained that the baseline population risk of fragility fracture for women around menopausal age in the UK is low and varies from one woman to another and their risk of fragility fracture is decreased while taking HRT.[1]

HRT is effective for the prevention of osteoporosis, but its beneficial effect on bone diminishes soon after stopping treatment[14] and may continue for longer in women who take HRT for longer.[1]

Because of the risks associated with long-term use, HRT should be used for prevention of osteoporosis only in women who are unable to use other medicines that are authorised for this purpose.[14]

Dementia

It should be explained to menopausal women that the likelihood of HRT affecting their risk of dementia is unknown.[1]

Loss of muscle mass and strength

There is limited evidence suggesting that HRT may improve muscle mass and strength.[1] Muscle mass and strength is maintained through, and is important for, activities of daily living.

HRT risk summary

Table 1 shows how the risks of HRT vary by different routes of administration.

Table 1: Risk summary by different routes of administration. Arrows indicate increased risk from baseline

	VTE	Type 2 diabetes	Stroke	CHD	Breast cancer	Ovarian cancer	Endometrial cancer
Oral	↑		↑	↑Combined*	↑	↑	↑OE + uterus**
Transdermal				↑Combined*	↑	↑	↑OE + uterus**
Vaginal							

*Combined = with combined HRT using both an oestrogen and progestogen/progesterone. No increased risk found with oestrogen-only HRT.
**OE + uterus = increased risk was only found with oestrogen only HRT in women with a uterus and greatly reduced with the appropriate addition of progestogen/progesterone.

Other hormonal oestrogen-deficiency treatments

Tibolone

Tibolone is licensed for the treatment of oestrogen deficiency symptoms in postmenopausal women, more than one year after menopause, as well as the prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. The 2.5mg tablets are taken once daily.[15]

Prasterone

Prasterone is biochemically and biologically identical to endogenous dehydroepiandrosterone (DHEA) and is converted to oestrogens and androgens.[8] It is available as a vaginal pessary, indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms that adversely affect the quality of life. The 6.5mg pessaries are used once daily, at bedtime.[16]

NICE NG23 identified new evidence for prasterone use for up to 3 months in the 2019 update.[1] However, the evidence suggested that prasterone was no more effective than vaginal moisturisers for vaginal dryness and dyspareunia.[17]

Ospemifene

Ospemifene is a selective oestrogen receptor modulator that has an oestrogen-like effect in the vagina, increasing the cellular maturation and mucification of the vaginal epithelium.[8] It is indicated for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy. The 60mg tablets are taken once daily.[18]

NICE NG23 identified new evidence for ospemifene in the 2019 update. The evidence indicates that it improves sexual function, vaginal dryness, and dyspareunia. Endometrial thickness was increased with ospemifene treatment for up to a year, but was not associated with endometrial hyperplasia. It was associated with more adverse events than placebo, but women were not more likely to stop treatment over 12 weeks.[17]

Please note: Tibolone, prasterone, and ospemifene are contraindicated in known, past or suspected breast cancer, known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer) and previous or current venous thromboembolism.[15,16,18]

Non-hormonal treatment

Clonidine 25 microgram tablets are licensed for the management of vasomotor conditions commonly associated with the menopause and characterised by flushing.[19] Clonidine may be used to reduce vasomotor symptoms in women who cannot take oestrogen, but may cause unacceptable side effects.[8] The dose is two 25 microgram tablets twice daily increased to three 25microgram tablets twice daily if needed after two weeks.[19] They cost £5.01 for 112 tablets.[20]

Information and Advice

Information should be given to menopausal women and their family members or carers (as appropriate) that includes:[1]

- An explanation of the stages of menopause
- Common symptoms and diagnosis
- Lifestyle changes and interventions that could help general health and wellbeing
- Benefits and risks of treatments for menopausal symptoms
- Long-term health implications of menopause
- Information on hormonal treatments for menopause, for example HRT, non-hormonal options, for example clonidine and non-pharmaceutical treatment, for example CBT.

The NHS website provides a useful overview of menopause and women and their family members or carers (as appropriate) may be referred to this website which provides this information.[21]

It should be explained that, as well as a change in their menstrual cycle, women may experience a variety of symptoms associated with menopause, including vasomotor symptoms (for example, hot flushes and sweats), musculoskeletal symptoms (for example, joint and muscle pain), effects on mood (for example, low mood), urogenital symptoms (for example, vaginal dryness) and/or sexual difficulties (for example, low sexual desire).[1]

Information on menopause should be provided in different ways to help encourage women to discuss their symptoms and needs.[1]

Women who are likely to go through menopause as a result of medical or surgical treatment (including women with cancer, at high risk of hormone-sensitive cancer or having gynaecological surgery) should be offered support and information about menopause and fertility before they have their treatment, along with referral to a healthcare professional with expertise in menopause.[1]

Contraception

The Faculty of Sexual & Reproductive Healthcare has issued guidance on contraception for women aged over 40 years. Information about contraception should be provided to women who are in the perimenopausal and postmenopausal phase.[22]

Women should be informed that contraception does not affect the onset or duration of menopausal symptoms but may mask the signs and symptoms of menopause.[22]

Can HRT be used alongside or in place of contraception?

Women using combined sequential HRT (oestrogen and progestogen/progesterone) should be advised not to rely on this for contraception. If women are still perimenopausal or their menopausal status is uncertain, effective contraception should be maintained in conjunction with combined sequential HRT if women are sexually active.[22]

Combined hormonal contraception should not be used in combination with HRT, however it can be used in eligible women under 50 as an alternative to HRT for relief of menopausal symptoms and prevention of loss of bone mineral density.[22]

Progestogen-only pills, depot injectables and implants are safe to use as contraception alongside combined sequential HRT. For progestogen-only depot injectables, consider changing to a lower-dose option.[22]

The Mirena® 52mg levonorgestrel intrauterine system (IUS) can be used as contraception alongside an oral or transdermal oestrogen of choice.[22,23] There have been no studies on the newer lower dose (19.5mg and 13.5mg) levonorgestrel intrauterine systems (Kyleena® and Jaydess® respectively) so these cannot be recommended currently.[24,25] The Mirena IUS should be removed (and replaced if required) after four years if being used for protection from endometrial hyperplasia during oestrogen replacement therapy and after five years if being used for contraception.[23]

When should contraception be stopped?

In general, all women can cease hormonal contraception at the age of 55 as spontaneous conception after this age is exceptionally rare, even in women still experiencing menstrual bleeding. If a woman aged 55 or over does not wish to stop a particular method, consideration can be given to continuation providing the benefits and risks for her as an individual have been assessed and discussed with her. However, intrauterine contraception should not be left in situ indefinitely after it is no longer required as it could become a focus of infection. Health care professionals should discuss sexually transmitted infections (STIs) and sexual health with women over 40. This population should be advised about condom use and protection from STIs even after contraception is no longer required.[22]

Premature ovarian insufficiency

The woman's clinical history should be taken into account (for example, previous medical or surgical treatment) and family history when diagnosing premature ovarian insufficiency.[1]

Premature ovarian insufficiency should be diagnosed in women aged under 40 years based on menopausal symptoms, including no or infrequent periods (taking into account whether the woman has a uterus) and elevated FSH levels on two blood samples taken four to six weeks apart.[1] It should not be diagnosed on the basis of a single blood test and anti-Müllerian hormone testing should not be routinely used for diagnosis.[1]

If there is doubt about the diagnosis of premature ovarian insufficiency, the woman should be referred to a specialist with expertise in menopause or reproductive medicine.[1]

Sex steroid replacement with a choice of HRT or a combined hormonal contraceptive should be offered to women with premature ovarian insufficiency, unless contraindicated (for example, in women with hormone-sensitive cancer).[1]

The following should be explained:[1]

- The importance of starting hormonal treatment either with HRT or a combined hormonal contraceptive and continuing treatment until at least the age of natural menopause (unless contraindicated).
- That the baseline population risk of diseases such as breast cancer and cardiovascular disease increases with age and is very low in women aged under 40.
- That HRT may have a beneficial effect on blood pressure when compared with a combined oral contraceptive.
- That both HRT and combined oral contraceptives offer bone protection.
- That HRT is not a contraceptive.

Women with premature ovarian insufficiency and contraindications to hormonal treatments should be given advice, including on bone and cardiovascular health, and symptom management.[1]

Referral to healthcare professionals who have the relevant experience to help women with premature ovarian insufficiency manage all aspects of physical and psychosocial health related to their condition should be considered.[1]

Complementary therapies

Women who wish to try OTC complementary therapies should be made aware that the quality, purity and constituents of products may be unknown.[1]

There is some evidence that St John's wort may be of benefit in the relief of vasomotor symptoms in women with a history of, or at high risk of, breast cancer.[1] However, there is uncertainty about appropriate doses, persistence of effect, variation in the nature and potency of preparations and potential serious interactions with other drugs (including tamoxifen, anticoagulants and anticonvulsants).[1]

There is also some evidence that isoflavones or black cohosh may relieve vasomotor symptoms and this should be explained. However, there are multiple preparations available and their safety is uncertain, different preparations may vary and interactions with other medicines have been reported.[17]

Soy (isoflavone), red clover, black cohosh, vitamin E or magnetic devices should not be offered to treat menopausal symptoms in women with breast cancer.[10]

Review and Referral

Each treatment for short-term menopausal symptoms should be reviewed at three months to assess efficacy and tolerability and annually thereafter unless there are clinical indications for an earlier review (such as treatment ineffectiveness, side effects or adverse events).[1]

Women should be referred to a healthcare professional with expertise in menopause if treatments do not improve their menopausal symptoms or they have ongoing troublesome side effects.[1]

Referral to a healthcare professional with expertise in menopause should be considered if there are menopausal symptoms and contraindications to HRT or there is uncertainty about the most suitable treatment options for their menopausal symptoms.[1]

The importance of keeping up to date with nationally recommended health screening should also be highlighted.[1]

Synthetic versus 'body identical' HRT

There are several 'body identical' (also commonly referred to as 'bioidentical') versions of HRT available as licensed preparations in the UK, including Bijuve® (estradiol and progesterone) oral capsules and Utrogestan® (progesterone) micronised oral capsules.[26,27]

Current evidence from large observational studies and case-controlled studies suggests that micronised progesterone and dydrogesterone are unlikely to increase the risk of venous thrombosis and are associated with a lower risk of breast cancer compared to that noted with oral progestogens.[28-30]

Regarding the unlicensed compounded (special order, commonly known as 'specials') versions of 'body identical' or 'bioidentical' HRT, the efficacy and safety of these unregulated compounded preparations are unknown.[1]

Cost and savings

There is a significant difference in cost between HRT products available. Table 2 below illustrates the cost differences.

Table 2: HRT product and price comparison, February 2022

HRT[8,20,32]	Cost per 28 days supply [20,31]
Unopposed oestrogen – oral	
Premarin® 1.25mg tablets (conjugated oestrogens)	£1.19
Premarin® 0.625mg tablets (conjugated oestrogens)	£1.34
Estradiol 1mg or 2mg tablets	£1.69
Bedol® 2mg tablets (estradiol)	£1.69
Elleste Solo® 1mg or 2mg tablets (estradiol)	£1.69
Premarin® 0.3mg tablets (conjugated oestrogens)	£2.02
Zumenon® 1mg or 2mg tablets (estradiol)	£2.30
Progynova® 1mg or 2mg tablets (estradiol valerate)	£2.43
Unopposed oestrogen – transdermal	
Evorel® 25mcg/24hrs patches (estradiol)	£3.42
Evorel® 50mcg/24hrs patches (estradiol)	£3.88
Evorel® 75mcg/24hrs patches (estradiol)	£4.12
Evorel® 100mcg/24hrs patches (estradiol)	£4.28
Sandrena® 500mcg gel sachets (estradiol)	£5.08
Estraderm MX® 25 25mcg/24hrs patches (estradiol)	£5.50
Estraderm MX® 50 50mcg/24hrs patches (estradiol)	£5.51
Sandrena® 1mg gel sachets (estradiol)	£5.85
Estradot® 25mcg/24hrs patches (estradiol)	£5.99
Estradot® 37.5mcg/24hrs patches (estradiol)	£6.00
Estradot® 50mcg/24hrs patches (estradiol)	£6.02
FemSeven® 50 50mcg/24hrs patches (estradiol)	£6.04
Progynova TS® 50 50mcg/24hrs patches (estradiol)	£6.30
Estraderm MX® 75 75mcg/24hrs patches (estradiol)	£6.42
Estraderm MX® 100 100mcg/24hrs patches (estradiol)	£6.66
Progynova TS® 100 100mcg/24hrs patches (estradiol)	£6.90
FemSeven® 75 75mcg/24hrs patches (estradiol)	£6.98

Unopposed oestrogen – transdermal	**Cost per 28 days supply** [20,31]
Estradot® 75mcg/24hrs patches (estradiol)	£7.00
Estradot® 100mcg/24hrs patches (estradiol)	£7.27
FemSeven® 100 100mcg/24hrs patches (estradiol)	£7.28
Oestrogel® Pump-Pack 0.06% gel (estradiol)	£4.20 - £8.40
Lenzetto® 1.53mg/dose transdermal spray (estradiol)	£3.45 - £10.35
Combined HRT – oral (continuous and sequential/cyclical, as indicated)	
Premique Low Dose® 0.3mg/1.5mg modified-release tablets (conjugated oestrogens + medroxyprogesterone acetate) – continuous HRT	£2.17
Elleste Duet® 1mg tablets (estradiol 1mg tablets and estradiol 1mg + norethisterone acetate 1mg tablets) – sequential HRT	£3.07
Elleste Duet® 2mg tablets (estradiol 2mg tablets and estradiol 2mg + norethisterone acetate 1mg tablets) – sequential HRT	£3.07
Clinorette® tablets (estradiol 2mg tablets and estradiol 2mg + norethisterone 1mg tablets) - sequential HRT	£3.08
Trisequens® tablets (estradiol 2mg tablets, estradiol 2mg + norethisterone acetate 1mg tablets and estradiol 1mg tablets) - sequential HRT	£3.70
Kliofem® tablets (estradiol 2mg + norethisterone acetate 1mg) – continuous HRT	£3.81
Novofem® tablets (estradiol 1mg tablets and estradiol 1mg + norethisterone acetate 1mg tablets) – sequential HRT	£3.81
Kliovance® tablets (estradiol 1mg + norethisterone acetate 500mcg) - continuous HRT	£4.40
Femoston® 1/10mg tablets (estradiol 1mg tablets and estradiol 1mg + dydrogesterone 10mg tablets) – sequential HRT	£5.39
Femoston® 2/10mg tablets (estradiol 2mg tablets and estradiol 2mg + dydrogesterone 10mg tablets) - sequential HRT	£5.39
Elleste Duet Conti® tablets (estradiol 2mg + norethisterone acetate 1mg) – continuous HRT	£5.67
Tridestra® tablets (estradiol valerate 2mg tablets and estradiol valerate 2mg + medroxyprogesterone acetate 20mg tablets) - sequential HRT	£6.30
Indivina® 1mg/2.5mg tablets (estradiol valerate/medroxyprogesterone acetate) – continuous HRT	£6.86
Indivina® 1mg/5mg tablets (estradiol valerate/medroxyprogesterone acetate) – continuous HRT	£6.86
Indivina® 2mg/5mg tablets (estradiol valerate/medroxyprogesterone acetate) - continuous HRT	£6.86
Bijuve® 1mg/100mg oral capsules (1mg estradiol hemihydrate and 100mg progesterone) - continuous HRT	£8.14
Femoston-conti® 0.5mg/2.5mg tablets (estradiol (as hemihydrate)/dydrogesterone) - continuous HRT	£8.14
Femoston-conti® 1mg/5mg tablets (estradiol (as hemihydrate)/dydrogesterone) - continuous HRT	£8.14

Combined HRT – transdermal (continuous and sequential/cyclical, as indicated)	Cost per 28 days supply [20,31]
Evorel Sequi® patches (estradiol hemihydrate 50mcg/24 hrs; estradiol 50mcg and norethisterone acetate 170mcg/24 hrs) – sequential HRT	£11.09
Evorel® Conti patches (estradiol hemihydrate 50mcg + norethisterone acetate 170mcg/24 hrs) – continuous HRT	£12.41 - £13.00
FemSeven Sequi® patches (estradiol 50mcg/24 hrs and estradiol 50mcg + levonorgestrel 10mcg/24 hrs) - sequential HRT	£12.51 - £13.18
FemSeven Conti® patches (estradiol 50mcg and levonorgestrel 7mcg/24 hrs) – continuous HRT	£14.71 - £15.48
Add-on progestogen	
Provera® 2.5mg tablets (medroxyprogesterone acetate) 2.5mg daily	£1.72
Climanor® 5mg tablets (medroxyprogesterone acetate) 10mg daily for last 14 days of each 28-day cycle	£3.27
Provera® 5mg tablets (medroxyprogesterone acetate) 5mg daily	£3.45
Provera® 10mg tablets (medroxyprogesterone acetate) 10mg daily for 14 days per 28-day cycle	£3.45
Utrogestan® micronized 100mg capsules (progesterone) 200mg at bedtime for 12 days per 28-day cycle or 100mg at bedtime from day 1 to day 25 per 28-day cycle.	£4.10 - £4.28
Mirena® levonorgestrel 20micrograms/24hours intrauterine device – changed every four years	£1.62
Vaginal oestrogen preparations	
Ovestin® 0.1% cream (estriol)	£1.19 - £4.15
Vagirux® 10mcg vaginal tablets (estradiol)	£3.78 - £8.51
Imvaggis® 30mcg pessaries (estriol)	£4.46 - £12.82
Blissel® 50mcg/g vaginal gel with applicator (estriol)	£5.04 - £14.49
Vagifem® 10mcg vaginal tablets (estradiol)	£5.57 - £12.54
Estriol 0.01% cream with applicator	£12.50 - £43.73
Other hormonal oestrogen-deficiency treatments	
Tibolone 2.5mg tablets	£5.87
Livial® 2.5mg tablets (tibolone)	£10.36
Intrarosa® 6.5mg pessaries (prasterone)	£15.94
Senshio® 60mg tablets (ospemifene)	£39.50

Cost-effective HRT choices

Vaginal preparations

Vaginal moisturisers and lubricants can be important in helping women with vaginal symptoms.[1] These can be purchased OTC and should be recommended.

When vaginal and/or bladder symptoms of urogenital atrophy predominate, vaginal oestrogen alone can be used. It can also be used alongside systemic HRT and/or vaginal moisturisers or lubricants if required.[1]

Currently, the most cost-effective preparation available is Estriol (Ovestin®) 0.1% cream.

Although estriol is now available generically as a 0.01% cream, this is considerably more expensive and delivers the same dose per applicator as the 0.1% cream and therefore should not be routinely prescribed.[8,31]

Systemic HRT (transdermal or oral administration)

If, after discussion of the individual risks and benefits, HRT is deemed appropriate, the following options are the most cost-effective, depending on the preferred route of administration.

Oral route of administration for oestrogen

Women without a uterus:

- Premarin® 0.625mg or 1.25mg tablets
- Estradiol 1mg or 2mg tablets
- Elleste Solo® 1mg or 2mg tablets
- Bedol® 2mg tablets

Women with a uterus*:

- Premique Low Dose® 0.3mg/1.5mg modified-release tablets (continuous HRT)
- Elleste Duet® 1mg or 2mg tablets (sequential HRT)

Transdermal route of administration for oestrogen

Women without a uterus:

- Evorel®) 25mcg/24hours, 50mcg/24hours, 75mcg/24hours or 100mcg/24hours transdermal patches
- Sandrena® 500mcg or 1mg gel sachets (estradiol)

Women with a uterus*:

- Evorel®) 25mcg/24hours, 50mcg/24hours, 75mcg/24hours or 100mcg/24hours transdermal patches **plus**
  - Provera® 2.5mg, 5mg or 10mg tablets (unlicensed use) or
  - Climanor® 5mg tablets or
  - Utrogestan® 100mg oral capsules
- Sandrena® 500mcg or 1mg gel sachets (estradiol) **plus**
  - Provera® 2.5mg, 5mg or 10mg tablets (unlicensed use) or
  - Climanor® 5mg tablets or
  - Utrogestan® 100mg oral capsules
- If adherence with a combination of transdermal and oral preparations is a concern:
  - Evorel Sequi® patches (sequential HRT)
  - Evorel® Conti patches (continuous HRT)

*If a Mirena® IUS is in situ, no additional progesterone is required and the woman can be treated as per 'women without a uterus'.

Micronised progesterone (e.g. Utrogestan®) is preferred for people with a high risk of breast cancer, venous thromboembolism or cardiovascular disease or in those who cannot tolerate synthetic progesterone.[26-28]

Savings

The potential switch options are outlined below (although clinicians may choose other options according to the clinical need of the patient). These include:

1. Review all women prescribed HRT annually to reassess dose, risks and the ongoing need for treatment, bearing in mind that the lowest possible dose should be used for the shortest possible time. Discontinue prescribing where the ongoing risks outweigh the benefits of treatment and ensure HRT is only prescribed for the relief of menopause symptoms that adversely affect quality of life.
2. Switch eligible women still requiring vaginal oestrogen to estriol (Ovestin®) 0.1% cream.
3. Switch eligible women still requiring systemic HRT to a cost-effective oral or transdermal oestrogen preparation (depending on risk assessment). For women with a uterus and no Mirena® levonorgestrel IUS in situ, a combination product with both oestrogen and progestogen/progesterone or appropriate add-on progestogen/progesterone should be prescribed, according to the manufacturer's recommended dosage (except if there is a family history of breast cancer – risks are finely balanced so seek advice).
4. Switch eligible women who have risk factors for VTE and still require HRT, to a transdermal oestrogen. If progesterone is also indicated, micronised 'body identical' progesterone should be prescribed, according to the manufacturer's recommended dosage.
5. Switch eligible women who have a high risk of breast cancer, cardiovascular disease or who cannot tolerate synthetic progesterone, but still require progesterone, to micronised 'body identical' progesterone. This should be alongside an appropriate oestrogen preparation.
6. Ensure women with premature ovarian insufficiency or who have had a bilateral salpingo-oophorectomy are prescribed hormonal therapy in line with current recommendations up until the time they would have expected the natural menopause.
7. Ensure that where new initiation of HRT is clinically indicated for the relief of menopause symptoms that adversely affect quality of life, women are prescribed a cost-effective preparation appropriate for their needs, taking into account their individual risk factors and shared decision making.

Switch Savings

In England, Scotland and Wales, £122,217,140 is spent annually NHSBSA (Sep-Nov21) and Public Health Scotland (Sep-Nov21) on HRT.

Reviewing women on HRT and discontinuing 10% of prescribing where the ongoing risks outweigh the benefits of treatment could save £10,256,383 in England, £545,579 in Wales and £1,115,956 in Scotland annually. This equates to £16,929 per 100,000 patients.

Switching 50% of eligible women to a more cost-effective alternative* could save £33,456,186 in England, £1,773,341 in Wales and £3,860,460 in Scotland. This equates to £55,526 per 100,000 patients.

*Based on switching vaginal oestrogen to oestriol (Ovestin®) 0.1% cream; oral combination HRT to Premique Low Dose®; transdermal combination HRT to Evorel® plus Provera®; single oral oestrogen to Premarin®; single transdermal oestrogen to Evorel®.

Switching women prescribed vaginal lubricants and moisturisers to self care with purchase OTC could save £2,347,950 in England, £302,805 in Wales and £387,207 in Scotland. This equates to £4,315 per 100,000 patients.

Summary

As well as a change in menstrual cycle, menopause can involve a variety of associated symptoms, including vasomotor symptoms (for example, hot flushes and sweats), musculoskeletal symptoms (for example, joint and muscle pain), effects on mood (for example, low mood), urogenital symptoms (for example, vaginal dryness) and/or sexual difficulties (for example, low sexual desire).[1] It is important to take into account the individual risks and benefits of the different treatment options available to treat the symptoms of menopause and ensure evidence based, safe and cost-effective prescribing.[1]

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Additional PrescQIPP resources

Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-299-menopause/
Implementation tools	
Data pack	https://data.prescqipp.info/views/B299_Menopause/FrontPage?%3Aembed=y&%3Aiid=1&%3AisGuestRedirectFromVizportal=y

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