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Diagnosis and management of the menopause

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Menopause is the cessation of menstruation; it typically occurs at around 51 years of age. The postmenopausal phase of life is linked to a variety of health conditions, including osteoporosis, cardiovascular disease and cognitive decline. Beyond symptom control, hormonal replacement therapy (HRT) reduces the incidence of chronic health conditions. Some unfounded concerns and misunderstanding about the risks of HRT contribute to a low uptake of HRT, currently around 10% of menopausal women. This article highlights the symptoms of menopause and treatment options available. As the majority of menopause management occurs in primary care, a good understanding of the risks and benefits is paramount when guiding patients to make informed decisions about the treatment options.

Clinical case scenario

A 49-year-old woman presents suffering from hot flushes and irregular, heavy periods. She has no significant medical or surgical history. What is the most appropriate treatment?

- Continuous combined oral hormonal replacement therapy (HRT)
- Oestrogen-only HRT
- Sequential combined transdermal HRT
- Sequential combined oral HRT
- Vaginal oestrogen

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Prevalence and impact of the menopause

All women experience the menopause. However, when this happens and how an individual is affected varies. As of 2015, 1 500 000 women in the UK were estimated to be going through menopause (National Institute for Health and Care Excellence (NICE), 2015a).

The menopause is the cessation of menstruation for 12 months, with the average age being 51.4 years. However, the symptoms of menopause (see Table 1) begin 4 to 6 years before, when women are perimenopausal.

Women live a third of their life either peri- or postmenopausal, and the burden associated with untreated symptoms means that it is a significant health issue. A survey of 3890 women suggested 67% of peri- and postmenopausal women experience symptoms (Constantine et al., 2016) with 54% of women seeking medical input. Despite the impact on quality of life, there are still misconceptions about HRT that result in hesitation to initiate treatment.

Aetiology

Menopause reflects a reduction in ovarian follicles. Once the number of follicles reaches a critical level, ovulation ceases. This results in reduced oestrogen production and, due to the complex interaction of the hypothalamus–pituitary–ovarian feedback system, raised follicle-stimulating hormone (FSH).

As the concentration of oestrogen falls, the regularity, timing and heaviness of menstruation varies. The lack of formation of a corpus luteum and resulting progesterone can result in unopposed oestrogen secretion and profuse, irregular bleeding. The lack of oestrogen results in a variety of symptoms (see Table 1).

Table 1. Summary of symptoms of the menopause.

Type of symptom	Specific examples
Vasomotor symptoms	• Hot flushes • Night sweats
Psychological symptoms	• Mood changes • Anxiety/depression • Memory and concentration issues • Sleep disturbance • Loss of libido
Urogenital symptoms	Genital: • Vaginal dryness • Genital itching • Vulvo-vaginal atrophy Urinary: • Urinary frequency, urgency and incontinence • Increased urinary tract infection Sexual dysfunction: • Dyspareunia

Symptoms

An understanding of the symptoms and clinical presentation of the menopause allows for early intervention. This improves not only patient care, but also long-term health.

Vasomotor symptoms

Vasomotor symptoms (VMS) are the most prevalent symptom of menopause. Studies show that 85% of menopausal women suffer from some form of VMS (see Table 1) (Constantine et al., 2016). Hot flushes present even before the onset of menstrual disturbance and can last for approximately 7.4 years. They significantly impact quality of life and are one of the main reasons for seeking medical advice.

Oestrogen replacement is a highly effective treatment for VMS when given both orally and transdermally (Maclennan et al., 2004). If the patient does not wish to use HRT, then alternative therapies are available.

Cognitive and psychological symptoms

Menopausal women can present with an array of psychological symptoms that include forgetfulness and word-finding difficulties. Alongside these issues, women may report mood changes ranging from mood swings to anxiety and depression.

The exact pathophysiology behind cognitive deficits in menopause is not understood, and there is limited evidence regarding the protective effects of oestrogen therapy against dementia. Due to conflicting data, current recommendations are that HRT should not be initiated to reduce dementia risk (National Collaborating Centre for Women's and Children's Health (NCC-WCH, 2015)).

Women undergoing the menopausal transition are at higher risk of anxiety and depression. This is influenced by other factors including body mass index (BMI), unemployment, history of chronic disease and history of anxiety or depression. Although oestrogen is known to have a role in regulating neurotransmitters, evidence surrounding the use of HRT to improve mood is mixed.

NICE recommends considering HRT to alleviate low mood associated with menopause. This should be used in combination with non-pharmaceutical interventions such as cognitive behavioural therapy (NICE, 2015b (updated 2019)).

Selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) can be used in conjunction with HRT, as well as monotherapy for menopausal women diagnosed with anxiety and depression. However, there is little evidence that SSRIs/SNRIs alleviate

low mood associated with the menopause (NICE, 2015b (updated 2019)).

Sleep

Approximately 60% of menopausal women suffer from sleep disorders (Constantine et al., 2016). This is secondary to fluctuating hormone levels and VMS. Loss of sleep impacts quality of life and is linked to multiple chronic health conditions. Sleep quality improves with HRT, though this is often secondary to VMS improvement.

Urogenital symptoms

The urogenital tissues are particularly responsive to oestrogen. As a result of the declining levels during and after menopause, vulvovaginal atrophy occurs, leading to a range of symptoms (see Table 1). The incidence of these symptoms increases with age as the time without oestrogen increases (Constantine et al., 2016).

Sexual dysfunction

Approximately 40% of perimenopausal women report sexual dysfunction, which increases to 80% when postmenopausal (Dennerstein et al., 2002). Sexual dysfunction during menopause is secondary to reduced circulating sex hormones, vulvovaginal atrophy, lifestyle factors and mood changes. As the underlying aetiology is multifactorial, it can be challenging to treat. However, sexual dysfunction profoundly impacts quality of life and should be considered in all women experiencing menopause.

Long-term health effects

Cardiovascular disease

Cardiovascular disease (CVD) remains one of the leading causes of mortality and morbidity in the UK. Risk increases with age. However, the timing of the menopause may also influence CVD. Loss of oestrogen results in stiffened vessels and endothelial dysfunction.

Women who experience premature menopause spend a longer proportion of their lives without oestrogen's protective effects. As a result, women who transition through menopause when less than 45 years in age are at a 50% increased CVD risk. There is also a 10% increased risk of fatal coronary heart disease and all-cause mortality (Muka et al., 2016).

The Women's Health Initiative (WHI) suggested that HRT causes an increased risk of CVD in menopausal women (Rossouw et al., 2002). However, the link between HRT and CVD is not as straight-forward as previously thought.

The 'Timing Hypothesis' states that the influence of HRT on CVD varies depending on the time of initiation following menopause. Evidence shows that when HRT is started soon after menopause, it is protective against CVD, with some studies showing a 50% reduction in incidence (Schierbeck et al., 2012). However, this beneficial effect is lost if HRT is initiated in the postmenopausal period. When HRT is initiated in postmenopausal women, there is an increased risk of CVD (Marjoribanks et al., 2017). NICE recommends using risk tables to demonstrate the statistically insignificant risk of CVD associated with HRT to allow women to make an informed decision (see Table 2).

Osteoporosis

Osteoporosis is characterised by reduced bone density resulting in an increased risk of fragility fractures. One-in-three women are affected by osteoporotic fractures causing reduced quality of life and enormous economic burden (International Osteoporosis Foundation, 2017)

The loss of oestrogen during menopause results in the overstimulation of osteoclasts and under-stimulation of osteoblasts responsible for bone breakdown and formation, respectively.

Prevention of osteoporosis can be achieved with the early initiation of HRT. Women started on HRT in early menopause have an increased bone mass density compared with women who did not receive HRT. It is not recommended to use HRT to treat osteoporosis in older women, due to the associated risks. However, HRT is highly effective at preventing osteoporosis in young women, particularly women with premature ovarian insufficiency (POI).

Table 2. Absolute rates of breast cancer for different types of HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women.

		Difference in CVD incidence per 1000 menopausal women over 7.5 years (95% confidence interval) (baseline population risk in the UK over 7.5 years-26.3 per 1000) (Weiner et al., 2008)			
		Current HRT	**HRT <5 years**	**HRT 5–10 years**	**>5 years since stopping**
Oestrogen- only HRT	RCT estimate	6 fewer	No data available	No data available	6 fewer
Combined HRT	RCT estimate	5 more	No data available	No data available	4 more

Adapted from NICE (2015b).

For women with osteoporosis, alternative treatments include bisphosphonates. They are highly effective at reducing fragility fractures, but are notoriously difficult to take and have potentially severe side effects. Other alternatives include denosumab, selective oestradiol receptor modulators and parathyroid hormone peptides.

Recommended non-pharmacological interventions for osteoporosis prevention include calcium and vitamin D supplementation, smoking cessation and regular weight-bearing exercise (NICE, 2015b (updated 2019)).

Diagnosis

The menopause is a clinical diagnosis, and most women do not require laboratory investigation. NICE recommends that healthy women over the age of 45 years presenting with VMS and irregular periods should be diagnosed as perimenopausal. Women over the age of 45 years and with a 12-month history of amenorrhoea should be diagnosed as menopausal. In a woman without a uterus, the menopause should be diagnosed based on their symptoms. FSH should not be routinely used to diagnose menopause, as levels fluctuate throughout the transition.

FSH should only be used to diagnose menopause in women aged between 40 and 45 years with menopausal symptoms and women younger than 40 years in whom menopause is suspected. Other potential pathology should also be investigated (NICE, 2015b (updated 2019)).

Premature ovarian insufficiency

POI is the onset of menopause before the age of 40 years. POI affects approximately 1% of women under 40 years in age and 0.1% of women under 30 years in age. It can be secondary to genetic conditions, autoimmune disorders or infection. Iatrogenic causes include childhood cancer treatment, radiotherapy to the abdomen/pelvis or gynaecological surgery requiring the removal of both ovaries. In 90% of cases, no underlying cause is found; however, various risk factors (see Box 1) have been identified.

Box 1. Risk factors for POI.

- First-degree relative
- Ethnicity- risk greater in African-American and Hispanic ethnic groups
- Cigarette smoking.
- History of childhood cancer treatment
- Gynaecological surgery

There is strong heritability of the age of menopause; 10–15% of women with POI have a first-degree relative who also experienced early menopause (Van Kasteren et al., 1999). Additionally, there are statistically significant differences between ethnicities (Luborsky et al., 2003). Cigarette smoking also has an association (Chang et al., 2007).

POI is suspected in women less than 40 years in age and presenting with menopausal symptoms (see Table 2) and irregular or no periods. To confirm the diagnosis, two FSH samples are required, taken 4 to 6 weeks apart. Thyroid function and prolactin should also be assessed to rule out alternative pathology. POI is diagnosed if FSH levels are high on two occasions (NICE, 2015b (updated 2019)).

POI is associated with a reduced life expectancy of approximately 2 years. Women should be advised on lifestyle measures including weight loss, diet modification and regular exercise to reduce the risk of CVD and osteoporosis. To prevent osteoporosis, women should receive calcium and vitamin D supplementation (NICE, 2015b (updated 2019)).

The primary treatment for POI is the replacement of sex steroids to a physiological level. Treatment continues until the natural age of menopause and consists of HRT or the combined oral contraceptive. Women with POI require counselling on the benefits of HRT, including symptom management, bone protection and protection against CVD. Patients should be advised that the risk of breast cancer and CVD increases with age and treatment duration. However, the baseline risk in women less than 40 years in age is low (NICE, 2015b (updated 2019)).

Beyond the physical implications of POI, the psychological impact is profound. Patients require large amounts of support from health professionals and other organisations such as The Daisy Network.

Treatment options

The mainstay of any treatment for the menopause revolves around establishing the patient's priority. Only then can their treatment be tailored to the patient.

All women presenting with menopausal symptoms need to be fully informed about the condition and surrounding issues. This includes explaining the stages of menopause, symptoms (Table 1), beneficial lifestyle changes, long-term implications and benefits and risks of treatment (NICE, 2015 (updated 2019)).

HRT is the primary treatment for the menopause. It is usually helpful to discuss the risks associated with HRT early in the assessment, as this can inform the recommended options for HRT type and formulation.

Risks associated with HRT

Venous thromboembolism

Extensive observational studies have shown that oral HRT increases venous thromboembolism (VTE) risk two-fold, but the absolute increased risk is very small (from 6 per10 000 to 12 per 10 000 women per year). Lifestyle risk factors are often more significant, for example, smoking and obesity and it is therefore appropriate to put risk in this context. Patients may prefer to accept a slightly increased risk and adapt their lifestyle. A detailed history must be taken before initiation of HRT,

as the risk increases in the presence of risk factors, including a personal or close family history of VTE, smoking, recent surgery or hospitalisation or a BMI greater than 30 kg/m^2 (NCC-WCH, 2015).

Transdermal preparations avoid the hepatic first-pass metabolism, and therefore, do not increase VTE risk. There is also a correlation between progesterone preparation and VTE risk, with certain progesterones (such as medroxyprogesterone acetate (MPA)) carrying a greater risk. Micronised progesterone is not known to increase VTE risk (Canonico et al., 2010).

NICE recommends that when discussing HRT, women should be informed of the increased VTE risk with oral HRT preparations, and that the risk of a VTE in women on transdermal HRT is the same as the baseline population. For these reasons, transdermal preparations can be considered in women with an increased VTE risk, including those with a BMI greater than 30 kg/m^2. For women who are at high risk of a VTE (having personal or close family history) referral to a haematologist should be considered before starting HRT (NICE, 2015 (updated 2019)).

Stroke

There has been much conflicting evidence regarding the risk of stroke while taking HRT. However, evidence currently suggests that stroke risk is age-related and that baseline risk in women younger than 60 years in age is low (NICE, 2015 (updated 2019)). Oral HRT is associated with an increased risk of stroke (Canonico et al., 2016). This is dose-dependent, and therefore, the lowest possible dose should be used. The increased stroke risk is not seen when using transdermal preparations. Transdermal oestrogen preparations are a suitable alternative to oral oestrogen in women over 60 years in age or with a high stroke risk.

Breast cancer

The original WHI studies indicated what was thought to be a significant link between HRT and breast cancer (Rossouw et al., 2002). The increased risk was to the extent that the trial was ended early due to safety concerns. Following the publication of the WHI results, there was a large amount of public concern. However, re-analysis has shown that the link between HRT and breast cancer was not statistically significant. The study included older women (average age 63 years), a high proportion of obese patients and used high doses of older synthetic formulations of HRT.

Careful counselling is now required to overcome public perception resulting from the publicity surrouding old, misleading information and allow women to make fully informed decisions based on up-to-date information on the risks of HRT.

Recent large trials demonstrated an association between HRT and breast cancer, but the link between breast cancer and combined HRT relates to the formulation of progesterone with micronised progesterone conferring no increased risk (Fournier et al., 2008). Synthetic progestogens cause a small increase in the risk of breast cancer, similar to the risk associated with being overweight, sedentary or drinking two small glasses of wine daily. It is important to consider that although there is a small increased risk of breast cancer, there is not an increased risk of death from breast cancer with HRT. There is no increased risk of breast cancer from micronised progesterone, dydrogesterone or oestrogen-only HRT.

When discussing HRT, women should be made aware that the risk of breast cancer varies between each woman. This depends on risk factors including increasing age, obesity, personal or family history of breast cancer and the presence of the BRCA1/2 gene. Lifestyle factors such as smoking and alcohol intake should also be assessed (NCC-WCH, 2015).

Although there has been a demonstrated link between breast cancer and certain types of HRT, women need to be reassured that the baseline risk is low. Visual aids should be used to help understand the risk (see Fig. 1). It should be explained that the increased risk is related to treatment duration. Although the risk is reduced following cessation of HRT, a small increased risk remains. The risk should be then contemplated by the patient and balanced against the benefits of HRT therapy. If the perceived risk is too high, alternative treatments can be discussed.

Vaginal oestrogen is not known to cause an increased risk of breast cancer, so can be considered in women who have previously been treated for breast cancer (Rahn et al., 2014).

Hormone replacement therapy

HRT is the primary treatment for menopause. It is not only effective in treating symptoms, but also in preventing long-term health conditions. It can be confusing for doctors and patients when faced with the choices of formulation, dose and route of HRT. However, re-analysis of research and new formulations have confirmed that HRT is safe and can be tailored to the individual and prescribed indefinitely if preferred by the patient.

The variety of preparations available can be overwhelming and recent supply issues have further complicated matters. Often the decision is constrained by which formulation is currently available (updated information on availability can be found at https://thebms.org.uk – please note, membership of the society is not required for access to this information).

Preparation

HRT revolves around replacing the oestrogen that is no longer being produced. Oestradiol is the most potent and most commonly used option. Oestriol is less potent but used in local preparations of HRT.

One of the main factors when determining the preparation of HRT is whether the woman has a uterus. Unopposed oestrogen increases the risk of endometrial hyperplasia and cancer. This risk is mostly negated by the use of combined oestrogen and progesterone therapy.

In hysterectomised women, the protective effect of progesterone is not required, and continuous oestrogen therapy can be used (NICE, 2015b (updated 2019)).

Figure 1. Decision aid to help women understand the risks of breast cancer associated with HRT when compared to lifestyle risk factors.



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Regimen

The regimen of HRT depends on when the last menstrual period occurred. If less than a year prior, then a combined cyclical preparation should be used consisting of continuous oestrogen with sequential progesterone 12–14 days of the month. After a minimum of a year of HRT, or if the last menstrual period was over a year previously, women can be switched to continuous combined HRT. Continuous HRT has

the added benefit of a further reduced risk of endometrial cancer (Sturdee et al., 2000).

If breakthrough bleeding occurs following the switch from cyclical to continuous HRT and this does not settle within 3 to 6 months, then the patient can choose to restart the cyclical regimen for another year.

Route

HRT is available in a variety of different preparations and an informed decision requires communication and understanding of the risks and benefits of HRT. There is a twofold increased risk of VTE with oral HRT. For women with risk factors of VTE, alternative preparations should be considered. Transdermal and subcutaneous HRT avoids the first-pass metabolism of the liver and prevents the formation of coagulation factors associated with oral oestrogen therapy, reducing the risk of VTE (Canonico et al., 2010). Transdermal preparations are now first choice for many patients and specialists. Transdermal preparations are as effective in treating menopausal symptoms, but the patches themselves can be troublesome (Maclennan et al., 2004). Commonly reported issues include skin irritation or poor patch adhesion.

Vaginal oestrogen therapy is the primary treatment for urogenital symptoms, and can be offered to women already using oral/transdermal HRT. This can be administered via creams, rings, pessaries or tablets. Vaginal oestrogen therapy has very few adverse effects; it confers no known increased risk of breast cancer or endometrial cancer (Rahn et al., 2014). As such, it can be considered when systemic HRT is contraindicated (though this should be discussed with a specialist). Women should be advised that symptoms often reoccur when therapy stops.

Women should be advised that unscheduled bleeding is a common side effect of HRT within the first3 months. However, if it persists past 3 months, then it should be reported at the 3-month review. If bleeding occurs following the first 3 months, then prompt medical advice should be sort. Persistent bleeding warrants ultrasound investigation and potentially endometrial biopsy to rule out endometrial malignancy.

Side effects

Side effects of HRT are mainly secondary to progesterone (see Table 3). These can be difficult to tolerate and are one of the main factors affecting compliance (Panay and Studd, 1997).

Table 3. Side effects associated with HRT.

Psychological	Metabolic	Physical
Mood swings Anxiety Depressed mood Irritability	Adverse lipid changes	Weight gain Fluid retention Headaches Breast tenderness Hirsutism Acne

Adapted from Panay and Studd (1997).

The most common symptoms associated with progesterone are headaches, fluid retention and weight gain. Testosterone-derived progestogens can stimulate androgen receptors, resulting in androgenic side effects, including acne and hirsutism. Other progestogens may negatively impact lipid metabolism. In particular, MPA can cause a reduction in high-density lipoproteins.

Progesterone's systemic side effects can be reduced by using micronised progesterone, which is closer in structure to natural progesterone (Fitzpatrick et al., 2000). In addition, micronised progesterone has a lower risk of VTE and no breast cancer risk (after up to 5 years of use). These preparations are prescribed less often in primary care, but with greater awareness of the benefits this is likely to change.

Uterine and vaginal routes of progesterone, such as the Mirena levonorgestrel intrauterine system are licensed in the UK for use alongside oestrogen HRT. They can provide endometrial protection with fewer systemic side effects while also acting as contraception during the perimenopause. However, there seems to be no significant difference in breast cancer risk when compared to oral progesterone (Lyytinen et al., 2010).

Tibolone

If the side effects of HRT are proving too difficult for the patient, tibolone can be considered. Tibolone is a synthetic steroid that has no biological activity. However, its effects depend on the tissue to which it is delivered and its subsequent metabolites. In bone and vaginal tissue, the metabolites act as an oestrogen. In the endometrium, the metabolites act as a progestagen. In the brain and liver, the metabolites have androgenic properties. Tibolone is effective in treating symptoms of menopause, but is less effective than HRT. Adverse long-term effects include increased risk of stroke in women over 60 years of age and an increased risk of breast cancer in women with a history of breast cancer (Formoso et al., 2016).

Testosterone

Testosterone acts on many tissues throughout the body. As such, the reduction in testosterone during menopause has a wide variety of effects. Despite there being no direct correlation between testosterone levels and sexual dysfunction, testosterone therapy can significantly improve sexual function in menopausal women, but should be used in conjunction with oestrogen replacement (Somboonporn et al., 2005). However, it can have unpleasant side effects such as acne, hirsutism and voice changes and should be monitored.

Contraception and the menopause

Although fertility declines over the age of 40 years, effective contraception should be used until menopause to prevent unintended pregnancy. Perimenopausal women should be advised that HRT does not provide effective contraception and should use alternative methods. Contraception should continue for 2 years after the last period if younger than 50

years in age, and a year if older than 50 years in age (Faculty of Sexual and Reproductive Healthcare, 2019).

Alternatives to HRT

If HRT is contraindicated, then alternatives should be discussed: SSRIs/SNRIs, gabapentin and clonidine have been shown to reduce VMS. Venlafaxine appears to be the most effective, but has side effects such as nausea. It should be noted that alternative pharmacological treatments are less effective than HRT (Nelson et al., 2006).

Women should be advised that the safety and efficacy of alternative therapies are unknown, and the products are unregulated. They are not prescribed on the NHS for this reason. St John's Wort may help relieve VMS, but there is limited evidence regarding appropriate dose and potential interaction with other medications (NICE, 2015b (updated 2019)).

Vaginal moisturisers can be used to replace vaginal secretions and rehydrate vaginal tissue, but they are not as effective as vaginal oestrogen.

Lifestyle changes such as exercise and diet modification should be emphasised, due to the impact on the development of CVD and osteoporosis. There is some evidence that these modifications can alleviate mood changes associated with the menopause (Sternfeld et al., 2014).

Monitoring

Women should be reviewed at 3 months following initiation of HRT and 3 months after dose alteration. They can then be followed up annually when treatment is established. Women should be advised that they need to re-present earlier if there are concerns about effectiveness, side effects or adverse events. The importance of national screening programmes, particularly breast cancer screening and cervical screening programmes, should be reiterated (NICE, 2015b (updated 2019)).

Secondary care referral

Although most menopausal women can be managed in primary care, some patients may require specialist input. The criteria for referral to secondary care are outlined in Box 2. A 2-week wait referral for a pelvic ultrasound and endometrial biopsy should be made for women presenting with new irregular bleeding on an established HRT regimen.

Box 2. Criteria for referral to secondary care.

- Ongoing symptoms despite treatment
- Unable to tolerate the side effects of treatment
- HRT is contraindicated
- There is uncertainty about the most appropriate treatment
- Refer women with new irregular bleeding on an established HRT regimen for a 2-week wait appointment for pelvic ultrasound and endometrial biopsy

Source: NICE (2015b)

KEY POINTS

- Menopausal symptoms are varied and include vasomotor symptoms, psychological symptoms and genitourinary symptoms
- In women over 45 years in age and presenting with menopausal symptoms, FSH testing is not recommended and diagnosis should be made on symptoms alone
- The primary treatment of menopausal symptoms is HRT and patient choice should be informed by accurate information on the risks and benefits of HRT
- The risks of CVD, VTE, stroke and breast cancer need to be explained and the use of visual aids can be helpful
- In women with risk factors for VTE, transdermal preparations should be used
- Women with persistent symptoms, problematic side effects or contraindications to HRT require secondary care referral

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