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MANAGEMENT OF THE MENOPAUSE

- Menopause is a normal event in a woman's life; symptomatic management is needed in some cases**
- Lifestyle modification should be considered as an integral part of menopausal management**
- Hormone replacement therapy (HRT) is the most effective treatment for vasomotor symptoms**
- The benefit/risk ratio for HRT use is favourable close to the time of menopause**

INTRODUCTION

The menopause is defined as the permanent cessation of menstruation, determined retrospectively after 12 months of amenorrhoea.¹ Natural menopause results from ovarian failure and resultant oestrogen deficiency; the menopause can also be induced by surgery, chemotherapy or radiation.² **The menopause occurs at a median age of 51 years, varying from 40-58 years.**^{2,3} Various factors affect the age at which the menopause occurs including: smoking (may occur up to 2 years earlier), low socioeconomic status, age at menarche, parity, ethnicity, previous oral contraceptive use and family history.^{3,5} While the menopause is a normal event in a woman's life, some women experience health effects that may require healthcare professional input.^{6,7} This bulletin reviews the overall management of the menopause.

MENOPAUSAL SYMPTOMS

Table 1 summarises the different stages of the menopause and the associated prevalence of hot flushes;^{2,3,5} substantial variation exists, including skipping stages and moving back and forth between stages.

Table 1: Stages of menopausal transition and prevalence of hot flushes³

	Perimenopause (Duration~4 years) (menopausal transition)		Postmenopause	
	Early	Late	Early	Late
Menstrual cycle	Variable cycle length; 1 or 2 missed cycles/year	3 or more missed cycles/year	None	None
Endocrine	↔ ↑ FSH ↔ ↑ Estradiol	↑ FSH ↓ Estradiol	↑↑ FSH ↓↓ Estradiol	↑↑ FSH ↓↓↓ Estradiol
Prevalence of hot flushes (%)	40	65	50	10-15

The period prior to the menopause and for the first 12 months after the menopause is known as the perimenopause.⁸ It usually begins in the mid-late 40s lasting approximately 4 years.^{3,4,6,9} It is associated with changes in the menstrual cycle (intermittent ovulation and anovulation) and menopausal symptoms.⁹ The postmenopausal period refers to the time dating from 1 year after the final menstrual period.⁷ During the early menopause transition, oestrogen and follicle stimulating hormone (FSH) levels are usually normal or slightly raised; as the menopausal transition progresses, hormone levels are variable, but oestrogen levels fall markedly and FSH levels increase.³ Many symptoms have been attributed to the menopause, **however only vasomotor dysfunction (hot flushes and night sweats) and urogenital symptoms have been shown to be consistently associated with this time of life.**² These symptoms are directly related to a decrease in oestrogen levels and experienced to varying degrees by up to 75% of women.⁴ Other symptoms including urinary incontinence, insomnia, sexual dysfunction, depression, anxiety, labile mood, memory loss, fatigue, headache, joint pains and weight gain may be secondary to vasomotor and urogenital symptoms or related to other causes including thyroid dysfunction and ageing.^{2,4}

Hot flushes: are the most common symptoms of the menopause. These are most prevalent during the first year after the menopause.⁴ They are described as sudden feelings of warmth (on the chest, face and neck), often associated with perspiration, palpitations and anxiety, which are variable in frequency, duration and severity (lasting < 5 minutes).^{2,3} The mechanism causing vasomotor symptoms is not fully understood.^{2,3} They can be triggered by warm environments, hot food or drinks and stress, and can interfere with activities or sleep,^{2,3} leading to insomnia, irritability and difficulties with memory and concentration.⁴ **They last for 0.5 - 5 years in up to 90% of women who experience them,** after the natural menopause, but may persist for as long as 15 years in a small percentage of women.^{2,4} They last longer and are more severe in those women who have had a surgically induced menopause.^{4,8}

Urogenital symptoms: such as vaginal dryness, itching and dyspareunia are caused by physiological responses to low concentrations of oestrogen and androgens.^{2,4} They can lead to numerous symptoms including atrophic vaginitis, vaginal irritation, dysuria, nocturia and frequency, which can have an effect on quality of life.^{4,10} Unlike vasomotor symptoms, urogenital symptoms do not diminish over time.¹⁰

Other issues: In addition to the menopausal symptoms experienced by women, there are also long-term health impacts. The loss of ovarian function and the drop in oestrogen levels also affects other parts of the body in particular the bones and cardiovascular system.⁸

ASSESSMENT

Classic vasomotor symptoms in a woman in her late 40s to mid-50s do not require laboratory evaluation unless there is reason to suspect another cause.³ The routine measurement of FSH is not recommended as levels may fluctuate during the perimenopausal period and increased levels may occur in the presence of ovulatory cycles.⁵ They do not predict when the last menstrual period will occur and are not a guide to fertility status (see Table 1). Estimates of luteinising hormone, oestradiol, progesterone and testosterone are of no value in the diagnosis of ovarian failure.⁵

History taking should exclude other causes of vasomotor symptoms including: pregnancy, alcohol consumption, hyperthyroidism, narcotic withdrawal, pheochromocytoma, carcinoid, underlying malignancy and medications.³

Abnormal bleeding including postmenopausal bleeding, sudden change in menstrual pattern, intermenstrual bleeding or postcoital bleeding requires investigation.⁵

MANAGEMENT OF MENOPAUSAL SYMPTOMS

Non-Pharmacological Management

The best approach to the management of menopausal symptoms is to assess each woman's individual needs,³ including her risk factors for cardiovascular disease (CVD).⁵ **Lifestyle modifications such as a healthy diet, exercising regularly, maintaining a healthy body weight, limiting alcohol consumption and not smoking may be useful in relieving mild menopausal symptoms.**^{8,11,12} There is some evidence that women who are more active tend to suffer less from the symptoms of the menopause, however not all types of activity lead to an improvement in symptoms.¹¹ The best activity is aerobic, sustained, regular exercise; high-impact infrequent exercise may make symptoms worse. Avoidance or reduction of intake of alcohol and caffeine may reduce the severity and frequency of vasomotor symptoms. Moderate alcohol consumption seems to have no effect on hot flushes, however drinking more than 14 units per week is likely to increase hot flushes.⁸

Pharmacological Management

HORMONE REPLACEMENT THERAPY

Oestrogens have been used for over 50 years as a hormonal supplement for the treatment of menopausal women and are the **most effective treatment for vasomotor symptoms.**^{2-4,7} They are used in combination with progestogens for women with an intact uterus (to avoid the development of endometrial hyperplasia and subsequent carcinoma) whereas hysterectomised women should be given unopposed oestrogen.³⁻⁵

The main indication for hormone replacement therapy (HRT) is for the relief of menopausal symptoms.^{4,13} Oestrogens reduce the frequency and severity of hot flushes and are given systemically at the lowest dose for the shortest duration.⁷ Table 2 summarises the different types of HRT regimens.

Table 2: Types of HRT regimens

Perimenopausal	Postmenopausal
Intact uterus <ul style="list-style-type: none"> • combination of oestrogen and progesterone <ul style="list-style-type: none"> ◦ sequential <i>(will result in a regular bleed)</i> 	Intact uterus <ul style="list-style-type: none"> • combination of oestrogen and progesterone <ul style="list-style-type: none"> ◦ sequential or continuous combined regimen <i>(associated with no bleed)</i> • tibolone
Hysterectomy <ul style="list-style-type: none"> • oestrogen alone 	Hysterectomy <ul style="list-style-type: none"> • oestrogen alone • tibolone

Combined oestrogen and progestogen can be given as a sequential (cyclical) or continuous regimen. The choice of which regimen to use will depend on whether the woman is perimenopausal or postmenopausal.⁸ The synthetic steroid tibolone (with progestogenic, androgenic and oestrogenic effects) is effective for the treatment of hot flushes.^{2,3,14,15} It is only suitable for postmenopausal women, and any bleeding while on tibolone needs to be investigated.¹⁵

Topical oestrogen therapy is effective for moderate to severe vaginal symptoms,^{5,16} and is considered more appropriate than systemic therapy in the absence of vasomotor symptoms.¹⁰ Atrophic vaginitis may respond to a short course (few weeks) of a topical vaginal preparation, repeated if necessary.¹³

Oestrogen given systemically in the perimenopausal and postmenopausal period, and tibolone given in the postmenopausal period are also effective for the prevention of osteoporosis however **other medicinal products should be used first-line for the management of osteoporosis.**^{13,17} HRT may be used in women with an early natural or surgical menopause (< 45 years) as they are at high risk of osteoporosis,^{13,18} however alternatives to HRT should be considered if osteoporosis is the main concern.¹³

Adverse effects: Oestrogen-related adverse effects, including fluid retention, bloating, breast tenderness and nausea, are often transient. Progestogen-related adverse effects, including fluid retention, breast tenderness, headaches and mood swings, may be more problematic.⁵ Options for persistent side-effects include reducing the dose, changing the HRT type or route of delivery. The most commonly reported side-effects are weight gain and poor cycle control resulting in discontinuation of HRT,^{2,5,19} if poor cycle control persists pelvic pathology needs to be excluded.⁵

Duration of use: Advice from most sources is to use the lowest dose of hormone for the shortest duration to give symptom relief.^{7,17} Maximum therapeutic response is usually achieved by 3 months.^{5,20} Short term systemic use over 2 - 3 years is clinically appropriate, as flushes disappear within a few years in about two thirds of women;^{5,7,20} **patients should be reviewed on an individual basis (every 6 - 12 months) with regular attempts to discontinue therapy.**²⁰ Observational data has shown that up to 50% of women stop HRT after 1 year of treatment and up to 75% stop it within 2 years.⁷ An Irish survey found that overall, 1 in 5 menopausal women receive HRT; this increases

to 3 in 10 in those aged 55 - 64 years, of which the majority are on HRT for < 4 years.⁶ One in 5 are on it for \geq 6 years.⁶ Women with premature ovarian failure can be given HRT until the approximate age of natural menopause (i.e. until 50 years).¹³ Discontinuing HRT can be a difficult time for women as many experience a temporary recurrence of symptoms.² There are no clear guidelines on the best way to stop HRT; many experts advise that it should be gradually reduced rather than stopping it abruptly.²⁰

Risks of Hormone Replacement Therapy

Over the last 10 years, there has been much controversy regarding HRT. The decision as to whether to start a woman on HRT needs to be taken at an individual level.¹⁸ Current evidence suggests that the benefit/risk ratio is favourable for women who initiate HRT close to the menopause (< 60 years) but is less favourable for older women with increasing time since the menopause.^{13,16,22,23} HRT should only be considered when an indication for therapy has been clearly identified, contraindications excluded and the potential benefits and risks discussed with the patient.¹⁶ It should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking and alcohol¹⁸ and is not recommended in women with a history of, or at high risk of CVD, breast cancer, unexplained vaginal bleeding, endometrial cancer, venous thromboembolism (VTE) and those with active liver disease.³

Observational studies from the early 1990s had suggested that HRT might be beneficial in reducing CVD,^{17,24} however evidence from studies published in 2002 (including the randomised controlled trial [RCT] the Women's Health Initiative [WHI] and Million Women's Study) identified possible risks associated with HRT.^{19,24-28} Since these studies were first published controversy continues in relation to the prescribing of HRT;⁷ it has been suggested that the discrepancy between the results of the earlier observational studies and the later studies may be partly explained by study design.²⁴ While most of the women in the earlier observational studies were < 55 years and within 2 - 3 years after the menopause at the time that HRT was initiated,²³ the mean age of women in the WHI study was 63 years.^{3,17} Table 3 outlines the main risks associated with HRT.

Table 3: Risks associated with HRT*¹³

Risk	Age range (years)	Background incidence (per 1,000 women not using HRT)		Additional cases per 1,000 women using oestrogen only		Additional cases per 1,000 women using combined oestrogen/progesterone	
		>5 years	>10 years	For 5 years use	For 10 years use	For 5 years use	For 10 years use
Breast cancer	50-59	10	20	2	6	6	24
	60-69	15	30	3	9	9	36
Endometrial cancer	50-59	2	4	4	32	NS**	NS
	60-69	3	6	6	48	NS	NS
Ovarian cancer	50-59	2	4	<1	1	<1	1
	60-69	3	6	<1	2	<1	2
Venous thromboembolism***	50-59	5		2		7	
	60-69	8		2		10	
Stroke	50-59	4		1		1	
	60-69	9		3		3	
Coronary vascular disease (CVD)	70-79	29-44		NS		15	

* excludes tibolone, ** not significant, *** may be lower risk of VTE by the transdermal route

Coronary vascular disease (CVD) – The current consensus is that there are no cardiovascular benefits of HRT for menopausal women.^{14,16,17,22,23,29} The relative risk of CVD during use of combined HRT is slightly increased; as the baseline risk of CVD is strongly dependent on age, the number of extra cases of CVD due to combined HRT is very low in healthy women close to menopause, but will rise with more advanced age.³⁰ RCTs found no increased risk of CVD in hysterectomised women using oestrogen-only therapy.³⁰ Trials are underway to evaluate if initiation of HRT in early menopause will delay the onset of CVD.³¹

Stroke - Evidence suggests that HRT increases the relative risk of stroke.^{13,14,16,17,21}

Venous thromboembolism (VTE) - Data from both observational and RCTs report an increased risk of VTE with oral HRT,^{16,17,23} (higher with combined HRT than oestrogen alone).¹⁶ The risk emerges in the first two years after commencing HRT.^{16,23} Analysis of the WHI study found that oestrogen/progesterone is associated with a doubling of the risk of VTE,²⁸ however the absolute risk was lower in those women initiating HRT at < 60 years than those who started HRT at > 60 years of age.¹⁶ The increased risk is also associated with other risk factors including obesity and factor V Leiden.^{16,28} Observational data suggest lower VTE risk with transdermal HRT than with oral HRT, but there is no comparative RCT data on this subject.^{16,23}

Breast cancer increases with combined HRT use beyond 3-5 years,^{14,16,20,21} however this effect is not seen in those who start HRT early for premature menopause.⁵ Evolving evidence suggests that the increased risk may be as a result of promotion of existing cancers.¹⁶ The WHI study did not demonstrate an increase in breast cancer for women taking oestrogen alone.

Endometrial cancer is increased with use of unopposed systemic oestrogen, which is reduced by the addition of progestogen.^{14,16,23}

Ovarian cancer - published data on the role of HRT and risk of ovarian cancer is conflicting.^{16,17} Observational studies have suggested an association between ovarian cancer and HRT,¹⁴ which if present occurs rarely, and after 5 years of use.¹⁶

Tibolone increases the risk of breast cancer but to a lesser extent than HRT.¹³ Limited data do not suggest an increased risk of VTE and there are insufficient data to draw a conclusion on the risk of CVD with tibolone.¹³ Tibolone is associated with an increased risk of stroke particularly in older women, and an increased risk of endometrial cancer.^{13,21,23} It may enhance the effects of anticoagulants such as warfarin.¹⁴

Practical issues

There are many different preparations of HRT available in Ireland; oestrogens are available in oral, transdermal, and vaginal preparations while progestogens are available in oral, transdermal and intrauterine formulations. Each woman's needs should be individualised with respect to individual symptoms and preference of formulation. The levonorgestrel intrauterine system, which was originally developed for contraception, is now licensed to provide the progestogenic component of HRT.^{5,32}

Contraception is an important topic which should also be discussed with a menopausal woman with menopausal symptoms. During the perimenopausal period, although women have reduced fertility, they still require contraception if they are sexually active.³³ It is only when the menopause has been confirmed that contraception can be stopped.⁹ Experts advise continued use of contraception for 2 years after the last menstrual period (LMP) in women < 50 years, and for 1 year after the LMP for women over 50 years.^{9,34} Many women have their menopause masked by the use of hormones (contraceptive or HRT).^{9,34} **It is important to advise women that HRT is not a form of contraception.** The decision on choice of contraceptive needs to be taken on an individual risk/benefit level.^{9,33} (Guidelines from the UK Faculty of Sexual & Reproductive Healthcare on contraception for women > 40 years are available on <http://www.ffprhc.org.uk/>). In general, women can be advised to stop hormonal contraception at the age of 55 years as most (95.9%) will be menopausal at this stage.⁹

Other issues Androgens (e.g. testosterone) have been used to improve libido in women, however specialist advice is recommended as they are not successful in all women and other factors may be involved.^{5,7,20} Testosterone patches are authorised only for women with reduced libido who have had a surgical menopause and are receiving concomitant oestrogen therapy.³⁵

NON-HORMONAL THERAPIES

Due to concerns about the adverse effects of oestrogen following the WHI and Million Women's studies, there has been increased interest in non-hormonal therapies for menopausal symptoms.^{2,36} Many of these medicinal products are unlicensed and are less effective than oestrogen;³⁷ their use should be restricted to highly symptomatic women who cannot take oestrogen.³⁸

Clonidine is the only non-oestrogen-based preparation licensed for menopausal flushing.^{12,37,39} It is a centrally acting alpha-adrenoceptor agonist, which has adverse effects including dry mouth, sedation, dizziness, nausea and nocturnal restlessness.³⁷ It should be used with caution in conditions including cerebrovascular disease, coronary insufficiency, heart failure and renal failure; treatment should be discontinued gradually.³⁹

Selective serotonin reuptake inhibitors (SSRIs) and **serotonin-norepinephrine reuptake inhibitors (SNRIs)** which are unlicensed for menopausal symptoms, have been shown to be effective in reducing vasomotor symptoms in short-term studies, however, the **long-term safety of SSRIs and SNRIs needs further evaluation.**^{18,36,38} The mechanism of action is unknown: it has been hypothesised that temperature increases associated with hot flushes could be linked to an overloading of serotonin-receptor sites in the hypothalamus.³⁶ Evidence suggests that fluoxetine, paroxetine, citalopram and venlafaxine are effective in reducing the frequency and severity of hot flushes,^{11,36,37} with the SNRI venlafaxine showing the most convincing data.¹¹ Side effects include gastrointestinal symptoms and sexual dysfunction.³⁷

Gabapentin which is unlicensed, has shown modest efficacy in the treatment of hot flushes both in women with a history of breast cancer and those without.^{3,36,40} The mechanism of action in reducing hot flushes is unclear.³⁶ Side-effects include dry mouth, dizziness and drowsiness.³⁷

NON-PRESCRIBED THERAPIES

Menopausal women have been known to use complementary therapies including herbal therapies, as they are perceived to be a safe alternative to traditional hormone therapies.³⁷ Evidence does not suggest that these therapies improve menopausal symptoms and a major concern is that **complementary therapies may have pharmacological actions**, that may cause unwanted effects including potentially dangerous interactions with medicines.^{2,37} A European Directive has been introduced requiring herbal medicinal products for human use to be registered in the coming years.⁴¹

Phyto-oestrogens are plant substances that have effects similar to those of oestrogens.³⁷ The main sources are **soy** and **red clover**. The results from clinical trials involving soy are contradictory and difficult to evaluate owing to variation in soy preparations, dosages, duration of treatment and interindividual differences in isoflavone metabolism occurring in the general population. Soy extracts appear to be well tolerated, however endometrial hyperplasia has been reported in soy users in some studies. Red clover blossoms have been used for centuries in traditional herbal medicines. The majority of clinical trials do not support the efficacy of the red clover leaf extracts in alleviating hot flushes. While no serious adverse effects have been reported, there are concerns on the safety of using semi-purified isoflavones in women with a history of breast cancer.³⁷

Black cohosh is used widely to alleviate menopausal symptoms, however there are conflicting results on its efficacy in this setting.^{34,37,42} There are also safety concerns including **reports of hepatotoxicity** with its use.^{11,37}

There are **other herbal products** which have also been used as treatment for menopausal symptoms whose efficacy have not been proven including: evening primrose oil, dong quai, ginkgo biloba, ginseng and St John's Wort.^{11,37} Consideration should also be given to the possibility of herb-drug interactions, and concerns have arisen with: **Ginkgo biloba (interactions including warfarin, aspirin, thiazide)**, **ginseng (e.g. warfarin and phenelzine)** and **St John's Wort (e.g. ciclosporin, midazolam, tacrolimus, digoxin, warfarin, theophylline).**^{11,37}

SUMMARY

The menopause is a natural event in most women's lives with the majority of women experiencing very few or mild symptoms. However, some women do experience health effects and require healthcare professional input. Management of the menopause requires a holistic approach and lifestyle modifications should be considered the first step in menopausal symptom relief. HRT is the most effective pharmacological intervention for hot flushes and vaginal dryness. An individual benefit/risk profile should be conducted for every woman considering using HRT and the lowest effective dose should be used for the shortest time. For those requiring symptom relief who cannot use HRT there are non-hormonal therapies to consider, which although not as effective as HRT, may provide some relief from menopausal symptoms on an individual basis. The evidence base does not support the use of complementary therapies in relieving menopausal symptoms.

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