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MANAGEMENT OF MENOPAUSE

- **Assessment of menopausal women should consider factors including patient's age, symptoms and impact on quality of life, and risk for cardiovascular disease and osteoporosis**
- **In general, the benefits of hormone replacement therapy (HRT) outweigh the risks for most women with menopausal symptoms aged <60 years or within 10 years of menopause**
- **Transdermal oestrogen administration is associated with a lower risk of venous thromboembolism and stroke than oral administration**
- **Women should be informed that HRT is not a contraceptive method**

INTRODUCTION

Women's health is increasingly being recognised as a global health priority.[1] Menopause is caused by a depletion of ovarian follicles resulting in loss of the ovarian sex hormones, oestrogen and progesterone.[1-3] Some women may experience minimal or no menopausal symptoms while many experience menopausal symptoms that significantly impact their quality of life (QOL).[4] Menopause occurs at an average age of 51 years (range from 45 to 55 years),[1,5] while some women experience early or premature menopause. **With increasing life expectancy, the management of menopause and associated conditions (e.g. cardiovascular disease [CVD] and osteoporosis) is of growing importance, as many women will live for several decades after menopause.[1]** This bulletin updates a previous bulletin (NMIC 2017;23:2) on this topic.

TERMINOLOGY AND DEFINITIONS

Menopause is recognised as having occurred after 12 consecutive months of amenorrhoea (see table 1).[1]

Table 1: Terminology associated with menopause[1]

Menopause The permanent cessation of menstruation resulting from loss of ovarian follicular activity: this may be natural or induced		
Types of menopause		
Natural Recognised to have occurred when a woman has had 12 consecutive months without periods, due to loss of ovarian follicular activity for which no other obvious or physiological cause is present.	**Induced*** The cessation of menstruation which follows either surgical removal of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function (e.g. by chemotherapy or radiation).	**Premature or early** Menopause occurring before the age of 40 years is referred to as premature menopause or premature ovarian insufficiency (POI). Menopause that occurs between 40 and 45 years is termed early menopause
Stages of menopause		
• **Perimenopause –** the period of time beginning with the first clinical, biological and endocrinological features of approaching menopause, including vasomotor symptoms and menstrual irregularity, and ends 12 months after the last menstrual period • **Postmenopause** – the time dating from menopause onwards**		

* Induced menopause may be temporary or permanent; **- menopause can only be diagnosed retrospectively after 12 months of amenorrhoea

MENOPAUSAL SYMPTOMS

Menopausal symptoms (table 2), may result in a reduced QOL, and have a potential impact on relationships and working life.[5] **Surgical menopause results in a sudden loss of ovarian function, which often leads to acute and severe menopausal symptoms.[1,6,7]**

Table 2: Common menopausal symptoms and signs[8,9]

Central nervous system	Vasomotor symptoms - hot flushes, night sweats Mood disturbance - anxiety, depression Cognitive function - cognitive difficulties Sleep disturbance - delayed onset, frequent wakenings
Genitourinary tract	Vulvovaginal atrophy - dyspareunia Sexual dysfunction – loss of libido and sexual desire Urgency, stress incontinence, urinary frequency
Musculoskeletal system	Joint/muscle pain Loss of muscle mass - sarcopenia Loss of bone mass - osteopenia, increased risk of fractures

Vasomotor symptoms (VMS) (due to oestrogen loss) are the most common central nervous system symptoms and affect up to 85% of women; VMS may predate the onset of menopause, however their prevalence is highest in the first year following menopause.[1] The mean duration of VMS is >7 years, however approximately 20% of women may experience symptoms for up to 15 years.[5,8]

Genitourinary syndrome of menopause (GSM) occurs in up to 63% of women (due to oestrogen loss); GSM is frequently under-diagnosed (due to a reluctance to discuss the symptoms).[1,10-12] GSM commonly occurs 3 to 5 years following menopause (but may also predate menopause) and may continue lifelong.[1,13]

Other sequelae associated with menopause: Menopause is associated with an increased risk of osteoporosis;[1] it is estimated that one in three women aged >50 years will suffer an osteoporotic fracture.[1] **Menopause is also associated with an increased risk of CVD,** which cannot be distinguished from ageing.[14,15] Menopause is associated with central adiposity, insulin resistance and a pro-atherogenic lipid profile.[14,15]

ASSESSMENT and DIAGNOSIS

Assessment of menopause ideally should consider the individual's 1) age, 2) time since menopause onset, 3) menopausal symptoms and impact on QOL and ability to work, 4) menstrual history, 5) type of menopause (natural or induced), 6) need for contraception, 7) personal or family history of breast, ovarian, endometrial and colon cancer, venous thromboembolism (VTE), or migraine and 8) risk factors for CVD and osteoporosis.[1] Physical examination should include recording of weight, height and blood pressure, and women should be encouraged to take part in national screening programmes for breast and cervical cancer.[1]

The diagnosis of menopause is usually based on clinical history for most women aged >45 years.[5]

There is no requirement for follicle stimulating hormone [FSH] measurement to confirm the diagnosis in those aged >45 years.[2,5,16] FSH measurement (on day 2 to 5 of the menstrual cycle if menstruating) may be indicated in women aged 40 to 45 years with menopausal symptoms including change in menstrual cycle if diagnosis is uncertain, and in those with suspected premature ovarian insufficiency (POI) (see later section).[2,17,18] FSH levels should not be performed in those using combined hormonal contraception (CHC), HRT or high-dose progestogen for menstrual irregularity.[2,19] A normal FSH level does not exclude menopause.[20] If the diagnosis is inconclusive consider referral to/advice from a specialist menopause service and/or consider assessment for other causes.[5]

Other investigations may be considered to exclude conditions such as thyroid dysfunction, elevated prolactin and a pregnancy test (especially in women aged <45 years).[1]

MANAGEMENT

The management of menopause needs to be individualised to the patient and can include non-pharmacological and pharmacological approaches.[21] The woman ideally should be informed of: 1) the stages of menopause, 2) lifestyle changes and interventions that could help general health, 3) the benefits and risks of therapies for menopausal symptoms and 4) the long-term health implications of menopause.[2,4,5] **A menopausal woman ideally should be assessed and advised of her risk for CVD and osteoporosis, and encouraged to participate in national screening programmes such as breast and cervical cancer.[2,5,15,21]**

NON-PHARMACOLOGICAL APPROACHES

Women should be encouraged to have a healthy diet (low in saturated fat and salt, and rich in calcium and vitamin D), exercise regularly, stop smoking and review alcohol intake as a means to improving menopausal symptoms, and reducing CVD and osteoporosis risk.[1,4,15] Measures to manage VMS include dressing in layers and use of portable fans.[20] Alternative therapies including cognitive behavioural therapy, yoga and acupuncture may improve some menopausal symptoms and may be considered in those who do not wish to take, or are not suitable for HRT.[22]

PHARMACOLOGICAL MANAGEMENT

The pharmacological management of menopause includes both hormonal and non-hormonal therapies. The safety and efficacy of unregulated compounded bioidentical hormones are unknown,[4,23,24] and are not addressed in this bulletin.

Hormonal therapy

Hormone replacement therapy (HRT) includes oestrogens and progestogens; other hormonal therapies include tibolone and selective oestrogen receptor modulators (SERMs). Table 3 outlines systemic hormonal therapy regimens.

Table 3: Systemic hormonal therapy regimens currently marketed[6,8]

Perimenopausal	Postmenopausal
Intact uterus Combination of oestrogen and progesterone Sequential/cyclical regimen Oestrogen and 52mg LNG-IUS*	**Intact uterus** Combination of oestrogen and progesterone Sequential/cyclical or continuous regimen Oestrogen and 52mg LNG-IUS* Tibolone
Hysterectomy Oestrogen alone	**Hysterectomy**** Oestrogen alone Tibolone

LNG-IUS - levonorgestrel intrauterine system; * - only Mirena® is licensed for endometrial protection; **- note that a combination of oestrogen and progestogen may be considered for women with endometriosis who have had a hysterectomy

Systemic oestrogens are effective for the treatment of VMS and GSM;[23] those available in Ireland include oral and transdermal (patches, gels and spray) formulations, which are available as oestrogen alone or combined with a progestogen. **Women with an intact uterus should not be prescribed unopposed systemic oestrogen (including transdermal preparations); they require a progestogen to reduce the risk of endometrial hyperplasia and cancer.[2,21,25]** The choice of formulation, dose and route of administration should be individualised to the patient;[23] the aim is to use the lowest dose of oestrogen that is effective to control the symptoms.[23] **Transdermal administration of estradiol is associated with a lower risk of VTE and stroke compared to oral administration;[26-28]** it should be considered as first choice in women with related risk factors (e.g. women aged >60 years, obesity, dyslipidaemia).[5,9,14,26] Evidence does not suggest significant differences in the effectiveness of transdermal versus oral oestrogen.[23,29]

Progestogens should be administered with oestrogen in women with an intact uterus to reduce the risk of endometrial hyperplasia.[1] Progestogens available in combination formulations with oestrogen include medroxyprogesterone acetate, norethisterone acetate, drospirenone, and dydrogesterone.[30] Table 4 lists the progestogen only products that can be used together with oestrogen alone products. Women on high dose oestrogen may require higher progestogen doses.[5,24] There is some evidence (mainly observational studies) that micronised progesterone and dydrogesterone may have better risk profiles than other progestogens (see later sections).[8,14,31-41]

Table 4: Examples of progestogen only preparations for use in combination with systemic oestrogen in Ireland[18,30]*

Type	Regimen
Micronised progesterone	• 200mg orally daily 12 to 14 days a month (sequential/cyclical)** • 100mg orally daily (continuous combined)**
Dydrogesterone	• 10mg daily for 12 to 14 days a month (sequential/cyclical) • 5mg daily (continuous combined)**
Medroxyprogesterone acetate	• 10mg for 12 days a month (sequential/cyclical) • 5mg orally daily (continuous combined)***
Levonorgestrel IUS	• Mirena® 52mg (replace after 5 years if still required)

***-higher progestogen doses may be required with high dose oestrogen; **-authorised product is not marketed in Ireland but an exempt medicinal product is available; ***-off-label use; IUS-intrauterine system**

The Medicines Management Programme published prescribing guidance on medicinal products for HRT in response to product shortages (September 2022), which includes additional information on available HRT preparations.[30]

Contraindications for oral and transdermal HRT include unexplained vaginal bleeding, liver disease, prior oestrogen sensitive cancer (including breast cancer), prior coronary heart disease (CHD), stroke, or VTE; personal or inherited high risk of thromboembolic disease.[23]

Adverse effects: Most common adverse effects include nausea, bloating, weight gain, fluid retention, mood swings (progestogen related), breakthrough bleeding, headaches and breast tenderness.[23] There is an increased risk of gallstones, cholecystitis and cholecystectomy with HRT.[23]

Drug interactions: Information on drug interactions specifically with HRT is limited. Often evidence to support

such drug interactions relates to the use of oestrogens or progestogens for contraception.[42]

Topical (local) vaginal oestrogen is effective for the treatment of GSM.[4-6,23] There is minimal systemic absorption of oestrogen associated with its use and in general there is no requirement for progestogens,[1,4,6,23] however **any vaginal bleeding or spotting requires assessment.**[6] Treatment choices include estradiol (E2) (as a vaginal tablet/pessary), or the weaker oestrogen estriol (E3) (as a cream or a vaginal tablet/pessary).[13] A treatment effect is usually seen within the first few weeks, however the full beneficial effect may take longer.[13] Local vaginal oestrogen can be continued by symptomatic women for as long as required.[4,5,13]

Tibolone is a synthetic steroid with oestrogenic, progestogenic and weak androgenic activity that is indicated for menopausal symptoms only in postmenopausal women.[43] It is less effective than HRT[44] and is associated with an increased risk of breast cancer, endometrial cancer, stroke and VTE;[43] the risks may outweigh the benefits due to the increased risk of stroke in women aged >60 years.[18,43]

Selective oestrogen receptor modulators: There are a number of SERMs licensed for menopausal symptoms. Ospemifene (marketing status unknown in Ireland), which reduces symptoms of dyspareunia, urge incontinence and sexual dysfunction is indicated for the treatment of GSM in postmenopausal women.[6,10,21,23] However hot flushes can worsen in women using ospemifene and there is an increased risk of VTE.[6] Bazedoxifene (a SERM) combined with oestrogen (marketing status unknown) results in a modest reduction in VMS.[21,45,46]

Testosterone: Some guidelines recommend that testosterone supplementation (not authorised in Ireland for women) may be considered in women with low sexual desire, where other causes have been excluded and therapies (e.g. systemic HRT) have not been effective.[4,5,47]

Intravaginal dehydroepiandrosterone (DHEA) (not licensed in Ireland) is a vaginal pessary which improves VVA symptoms[6,13]. Current evidence suggests minimal symptom improvement with its use; a recent review advised that further evidence is required before it is routinely prescribed.[48]

Benefits and risks of hormonal therapy

There was a significant decline (19%) in the number of women prescribed HRT following the publication of a number of studies 20 years ago.[49] Recent evidence suggests that the risks associated with HRT vary with 1) the age at which HRT is started, 2) the type of HRT prescribed, and 3) individual risk factors of the woman.[2]

Systemic HRT is the most effective treatment for menopausal symptoms such as VMS and GSM.[1,2,4,23,50] It is also associated with an improvement in other symptoms including sleep disturbances, mood changes and overall QOL.[2-4,8,23] **The use of HRT and tibolone reduces the risk of osteoporotic fractures (hip, vertebral and total) by up to a third.**[51] While HRT may be considered for women with menopausal symptoms aged <60 years for the prevention and treatment of osteoporosis,[52] alternative medications are advised if osteoporosis is the main concern.[53,54]

Cardiovascular disease: The effect of HRT on CHD varies depending on when HRT is initiated.[23,45] **Current evidence suggests that HRT is associated with a reduced risk of CHD and all-cause mortality if initiated in women with menopausal symptoms aged <60years or within 10 years of menopause.**[26,31,55-60] Recent evidence suggests that the initiation or continuation of HRT in women aged ≥60 years has little effect on CHD or all-cause mortality.[26,55,56] These women are at higher absolute risk of CHD, stroke and VTE.[23]

Stroke: Oral oestrogen and tibolone are associated with a small increased risk of stroke;[26,45,55,56,60,61] **the risk of stroke increases with age and dose of oestrogen.**[8,27] Evidence (mainly observational) suggests that transdermal oestrogen ≤50 micrograms is associated with a lower risk of stroke than oral oestrogen.[26-28,31] Transdermal oestrogen is recommended as first-choice for women with risk factors for stroke and those aged >60 years.[8] Observational data suggests that HRT with micronised progesterone and dydrogesterone are associated with a lower risk of stroke.[8,58]

Venous thromboembolism: Oral HRT (oestrogen alone and combined oestrogen/progestogen) is associated with an increased risk of VTE, which increases with age.[4,6,26,55,56,62,63] Evidence (mainly observational studies) suggests that transdermal oestrogen is not associated with an increased risk of VTE;[8,26,27,31-35,41,62-64] it is recommended as the first choice route of administration for women with related risk factors (e.g. obesity, smoking).[1,4,8,31,40] Observational data suggests that micronised progestogen and dydrogesterone are less thrombogenic than other progestogens.[32-35,41]

Breast cancer: There is a small increased risk of breast cancer associated with HRT and tibolone;[4,23,36] the absolute excess risk of breast cancer over 10 years has been estimated to be 3 to 7/1000 women taking combined HRT.[37] There is evidence to suggest that the increased risk varies with the 1) type of HRT, 2) patient's age (lower risk for women in their 50s compared to older women), 3) duration of treatment (lower risk with therapy <5 years duration), 4) current or more recent treatment (higher risk than past use) and 5) woman's baseline risk of breast cancer.[23,36,65] Most studies report that in women aged >50 years, oestrogen alone HRT is associated with a marginal/no increased risk of breast cancer compared to combined HRT.[36,58,63,65-69] Some evidence suggests that the use of combined continuous HRT is associated with a higher risk of breast cancer than combined sequential HRT.[66] Observational evidence suggests that the risk of breast cancer is lower with micronised progesterone or dydrogesterone.[36-38]

Endometrial hyperplasia and cancer: Unopposed oestrogen replacement is associated with a significant increased risk of endometrial hyperplasia and cancer that is **both dose and duration dependent.**[23,24] The use of progestogens in women with a uterus, administered for 12 to 14 days in a sequential regimen (perimenopausal women) and daily in a continuous regimen (postmenopausal women) minimises this risk.[5,23,24,70,71] There is some evidence that long-term use (i.e. >5 years) of sequential HRT may be associated with a small increased risk of endometrial hyperplasia or cancer.[24,70,72]

Dementia: The association between HRT and dementia is unclear.[8,45] Based on available evidence women should be reassured that HRT is unlikely to increase the risk of dementia,[8] **however evidence does not support the use of HRT to reduce the risk of dementia.**[23,73]

Non-hormonal therapy

There are a variety of medicinal products for menopausal symptoms (**unlicensed indication in Ireland**), which may be useful for those not suitable for hormonal therapy, although such products are less effective than systemic oestrogens.[1]

Selective serotonin reuptake inhibitors (SSRIs), including paroxetine, fluoxetine, citalopram, escitalopram, and sertraline and **serotonin noradrenaline reuptake inhibitors** (SNRIs) including venlafaxine have been reported to reduce menopausal VMS (by up to 50%),[16,22,74] and may be recommended as alternative options for women with contraindications to HRT (e.g. breast cancer).[2,3,74] **Paroxetine and fluoxetine are potent cytochrome P450 2D6 inhibitors, which decrease the metabolism of tamoxifen and may reduce its anticancer effect**, therefore they should be avoided in tamoxifen users.[2,3,74]

Gabapentin has been shown to reduce menopausal VMS (up to 50%).[22,75] Evidence to support the use of pregabalin is lacking.[75] Use of gabapentin and pregabalin is associated with dependence and respiratory depression.[76-79]

Oxybutinin has been shown to reduce menopausal VMS, however adverse effects included dry mouth and urinary difficulties.[80] Evidence supporting the use of **clonidine** (which may cause unacceptable adverse effects) is contradictory.[3,22,53] Other non-hormonal agents (e.g. neurokinin antagonists) for the management of menopausal VMS are in development.[22]

Moisturisers and lubricants alone or in addition to vaginal oestrogen may be useful for symptoms related to VVA.[5,13] Lubricants provide immediate, short-term relief of vaginal dryness and dyspareunia,[6] while moisturisers hydrate dry mucosal tissue and can mimic normal vaginal secretions.[13] Note that oil-based lubricants can weaken condoms used as barrier contraception.[13]

Practical aspects to the use of HRT

Initiation: The decision to prescribe HRT, and also the type of HRT, dose and duration of use should be made on an individualised basis, with the benefits and risks (as outlined above) discussed with the patient.[4-6,8,23,31] **It is important to note that HRT is only indicated for symptomatic menopausal women.[73]** In general, the benefits of HRT outweigh the risks for most symptomatic women aged <60 years or within 10 years of the menopause.[1,4,6,23,73]

Women prescribed HRT should be reviewed 3 months after starting treatment (to assess menopausal symptoms, adverse effects of HRT, adherence to progestogen when indicated, weight and blood pressure) and thereafter on an annual basis.[5] Some women may experience unscheduled bleeding in the first few months after starting HRT, which may be resolved by modifying the progestogen, however unscheduled bleeding beyond 4 to 6 months should be assessed to exclude endometrial pathology.[23,24] After a minimum of 1 year on sequential HRT, women who wish to avoid a monthly withdrawal bleed may attempt a switch to a continuous combined regimen which aims to provide bleed-free HRT, and which also minimises the risk of endometrial hyperplasia.[24]

Duration: Recent guidelines recommend that arbitrary limits should not be placed on the duration of use of HRT;[5,8,23] continued use of HRT may be considered if appropriate in women aged >60 years.[5,23] Considerations include 1) the severity of VMS, 2) the patient's risk for CHD, stroke, VTE and breast cancer, and 3) the effectiveness of alternative non-hormonal interventions.[23] **Women with risk factors for CVD or VTE (e.g. obesity, smoking) and women aged >60 years who are assessed as appropriate to continue HRT should be advised to use transdermal rather than oral oestrogen and to use micronised progesterone or dydrogesterone where indicated.[5,6,23,31]**

Discontinuation: VMS return in approximately 50% of women when HRT is discontinued.[23] There is no consensus as to whether it is better to taper down HRT or to stop it abruptly.[1,23]

Premature ovarian insufficiency

Premature ovarian insufficiency (POI) (often referred to as premature menopause) occurs in women aged <40 years (incidence of 1%); it may be spontaneous or induced.[3] A diagnosis of POI is based on a combination of oligo/amenorrhoea for at least 4 months and persistently elevated FSH levels of >25 IU/L on two occasions >4 weeks apart[18,81] (some sources recommend elevated FSH levels of >30 IU/L for a diagnosis of POI[5]). Early menopause (aged 40 to 45 years) occurs in approximately 5% of women.[82] **In the absence of contraindications, HRT is recommended for women with POI and early menopause at least until the natural age of menopause (e.g. early 50s).[2-5,21,23]** Women with POI usually need higher doses of oestrogens compared to women >40 years.[3,20] Even asymptomatic women with POI or early menopause should consider HRT, as they are especially at increased risk of CVD, osteoporosis and cognitive impairment,[3,5,8,14,17,23,83-86] and HRT is likely to lower the long-term risk of CVD, prevent osteoporosis and may have a beneficial effect on cognitive function.[1,4,5,8] **The increased risk of breast cancer associated with HRT does not apply to women with POI or early menopause treated with HRT before the natural age of menopause;[4,23]** the increased risk occurs from the age of 50 years.[4] HRT plays a significant role in managing surgical menopause especially in women <45 years, who should be advised of the short and long-term effects of surgical menopause and of the management options including HRT.[7]

Ovulation is reported to occur in 50 to 75% of women with POI, with return of menses in 25 to 50% and pregnancy in 5 to 10%,[17] therefore fertility and contraception need to be discussed.[3,17,20] Ongoing contraception is recommended if pregnancy is not desired.[3,17] Fertility specialist review may be considered to discuss fertility options for appropriate women.[23]

Contraception and the menopause

Women should be informed that HRT is not a contraceptive method,[19] therefore sexually active women who are perimenopausal require contraception in addition to HRT.[19] Combined hormonal contraception (CHC) provides contraception and relief from VMS and may be suitable as an alternative to HRT for some women (e.g. those with POI or early menopause) or in the perimenopause depending on the benefit/risks of CHC, up to the age of 50 years.[5,17,21] Levonorgestrel intrauterine system, which may be used for endometrial protection as part of a HRT regimen, can be used for contraception (Mirena® should be replaced after 5 years, if used for endometrial protection).[19,87] Other progestogen-only methods of contraception can be used in addition to sequential HRT.[19] **Contraception is required for 2 years after the final menstrual period in women <50 years and for 1 year in those >50 years.[19]** In general, all women can cease contraception at the age of 55 years, as spontaneous pregnancies after this age are exceptionally uncommon.[19]

List of references available on ePublication on www.nmic.ie.
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