Hormone Replacement Therapy (HRT) Guidance and Treatment Pathway

Menopause is defined as a biological stage in a woman's life that occurs when she stops menstruating and reaches the end of her natural reproductive life. Usually it is defined as having occurred when a woman has not had a period for 12 consecutive months (for women reaching menopause naturally). The changes associated with menopause occur when the ovaries stop maturing eggs and secreting oestrogen and progesterone.[3]

Premature ovarian insufficiency is defined as menopause occurring before 40 years of age (also known as premature ovarian failure or premature menopause). It can occur naturally or as a result of medical or surgical treatment.[3]

A. Management of menopause

- Provide advice on lifestyle modifications to reduce menopausal symptoms (see table 1).
- HRT should only be prescribed in the context of a supportive consultation with their healthcare provider.
- Consideration should be given to the patient's full medical history, including personal, family and drug history and basic parameters e.g. height, weight, BMI and BP.
- SSRIs, SNRIs or clonidine should not routinely be offered as first-line treatment for vasomotor symptoms alone.
- Treatment should be adapted as needed, based on changing symptoms.

Table 1 Lifestyle modifications to reduce menopausal symptoms[2]

Symptom	Lifestyle modification
Hot flushes and night sweats	Regular exercise, weight loss (if applicable), wearing lighter clothing, sleeping in a cooler room, reducing stress, and avoiding possible triggers (such as spicy foods, caffeine, smoking, and alcohol).
Sleep disturbances	Avoiding exercise late in the day and maintaining a regular bedtime
Mood and anxiety disturbances	Adequate sleep, regular physical activity, and relaxation exercises
Cognitive symptoms	Exercise and good sleep hygiene

Premature ovarian insufficiency[1] (also referred to as premature menopause)

- Women should be offered a choice of HRT or a combined hormonal contraceptive unless contraindicated.
- Hormonal treatment should be started and continued until at least the age of natural menopause (51 years).

Discussion points for women with premature ovarian insufficiency:

- 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.
- HRT may have a beneficial effect on blood pressure when compared with a combined oral contraceptive
- Both HRT and combined oral contraceptives offer bone protection
- HRT is not a contraceptive – see Faculty of Sexual and Reproductive Healthcare guidance on 'Contraception for Women Aged Over 40 Years'

B. Hormone Replacement Therapy

Indications

- Relief of short-term vasomotor symptoms e.g. hot flushes
- Alleviate low mood as a result of the menopause
- Urogenital atrophy
- Premature ovarian insufficiency
- Prevention of osteoporosis in postmenopausal women at high risk of future fractures

Contraindications[4]

- Known or suspected oestrogen-dependent cancer.
- Undiagnosed vaginal bleeding.
- Untreated endometrial hyperplasia.
- VTE or history of recurrent VTE, unless the woman is already on anticoagulant treatment.
- Active or recent arterial thromboembolic disease
- Thrombophillic disorder or thrombophlebitis
- Untreated or unstable hypertension.
- Active liver disease with abnormal liver function tests.
- Acute Porphyria
- Pregnancy
- Dubin-Johnson and Rotor syndromes (monitor closely)

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Route of administration[1]

- Oral treatment is considered first in line where appropriate
- Transdermal therapy should be considered in the following instances:
  - ✓ Individual preference
  - ✓ Poor symptom control with oral treatments
  - ✓ Gastrointestinal disorders affecting oral absorption
  - ✓ Previous or family history of VTE
  - ✓ BMI > 30 kg/m^2
  - ✓ Variable blood pressure control, migraines, or gall bladder disease
  - ✓ Current use of hepatic enzyme inducing medication

Long term benefits and risks of hormone replacement therapy

Discuss the short-term (up to 5 years) and longer-term benefits and risks with women, prior to starting HRT.

Table 2: Summary of benefits and risks of HRT [1, 4]

Risk	Details
Venous thromboembolism (VTE)	✓ The risk of VTE is increased by oral HRT compared with baseline population risk ✓ The risk of VTE associated with HRT is greater for oral than transdermal preparations ✓ The risk associated with transdermal HRT given at standard therapeutic doses (under 50mcg/24h) is no greater than baseline population risk. ✓ In women with predisposing factors (e.g. personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks may exceed the benefits. ✓ **Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m^2** ✓ **Consider referring menopausal women at high risk of VTE (e.g. strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.**
Cardiovascular disease	✓ HRT does not increase cardiovascular disease risk when started in women aged under 60 ✓ HRT does not affect the risk of dying from cardiovascular disease ✓ HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease ✓ HRT with oestrogen and progestogen is associated with little or no increase in the risk of coronary heart disease.
Stroke	✓ Oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke. ✓ Tibolone increases the risk of stroke about 2.2 times from the first year of treatment.
Ovarian cancer	✓ Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer; this excess risk disappears within a few years of stopping.
Endometrial cancer	✓ The increased risk depends on the dose and duration of oestrogen-only HRT. ✓ In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously.
Breast cancer *(as per NICE guidance)*	✓ Oestrogen-only HRT is associated with little or no change in the risk of breast cancer ✓ HRT (oestrogen and progestogen) can be associated with an increased risk of breast cancer ✓ Any increase in breast cancer risk is related to treatment duration and reduces after stopping.
Osteoporosis	✓ Risk of fragility fracture is decreased while taking HRT and that this benefit is maintained during treatment but decreases once treatment stops and may continue for longer in women who take HRT for longer
Type 2 diabetes	✓ HRT (oral or transdermal) is not associated with an increased risk of type 2 diabetes. ✓ HRT is not generally associated with an adverse effect on blood glucose control. ✓ Consider HRT for menopausal symptoms in women with type 2 diabetes after taking comorbidities into account and seeking specialist advice if needed.

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Counselling points

- Advise women of the usual bleeding pattern to expect with their HRT
- Explain to women with a uterus that unscheduled vaginal bleeding is a common adverse effect of HRT within the first 3 months of treatment. Women should report this at 3-month review, or promptly if after first 3 months.[1]
- Reinforce the importance of adherence with therapy
- Remind women in the peri-menopause or with premenstrual ovarian insufficiency that that HRT is not a contraceptive and contraceptive precautions are still necessary[1]
- Discuss with women the importance of keeping up to date with nationally recommended health screening[1]

Poor symptom control

Possible cause	Management
Compliance	Counsel on importance of compliance – allow 3-6 months on therapy for full effect.
Oestrogen dose	Increase dose or change from oral to transdermal route.
Poor patch adhesion	Try alternative brand
Incorrect diagnosis	Review indications (e.g. thyroid disease) or refer.
Poor absorption	Consider transdermal route
Unrealistic expectations	Counsel patient
Drug interactions	Enzyme inducers lower the circulating levels of hormone e.g. barbiturates, phenytoin, carbamazepine. Change to non-oral route. Intra-Uterine Systems are not affected. Increased risk of thromboembolism with lenalidomide, thalidomide and pomalidomide

Management of side effects[2] - encourage persistence with treatment for 3 months (adverse effects may resolve)

Oestrogenic side effects		
System	**Side effect**	**Management**
Breast symptoms	Breast tenderness Breast enlargement	• May be alleviated by a low-fat, high-carbohydrate diet. • Reduce dose of oestrogen • Change to transdermal route (more stable oestrogen levels)
Gastrointestinal symptoms	Bloating Nausea	• Adjust timing of dose and take with food • Change route of administration
Other symptoms	Headache/Migraine Leg cramps	• For headache/migraine - change route of administration • Leg cramps may improve with lifestyle changes e.g. exercise and stretching calf muscles

Progestogenic side effects - *tend to occur in a cyclical pattern during the progestogen phase of cyclical hormone replacement therapy (HRT).*		
System	**Side effect**	**Management**
PMS like symptoms	Fluid retention Breast tenderness Lower abdomen pain Backache	• Change ***progestogen type*** from a more androgenic one (such as norethisterone and norgestrel) to a less androgenic one (such as medroxyprogesterone or dydrogesterone). • Changing ***route of delivery*** from oral to transdermal, vaginal, or intrauterine. (The levonorgestrel-releasing intrauterine system (IUS, Mirena®) is an alternative route of delivery of progestogen)[4] • ***Reduce the regimen*** of progestogen administration Progestogens can be taken for 10 to 14 days of each monthly sequential regimen, so swapping from a 14-day to a 10-day product may provide benefit. • Changing to a ***lower dose*** of progestogen • Reducing ***frequency of progestogen dosing*** by switching to a long-cycle regimen of progestogen for 14 days every 3 months (for women without natural regular periods).
Psychological symptoms	Depression Mood swings	
Other symptoms	Acne/greasy skin Headache	

Duration of treatment [1, 3]

- HRT should be continued for as long as it is of benefit, and improvement in quality of life outweighs risks.
- Offer gradual reduction of HRT to limit recurrence of symptoms in the short term (gradually reducing or immediately stopping HRT makes no difference to their symptoms in the longer term).

Contraception [4]

See the Faculty of Sexual and Reproductive Healthcare guidance on *'Contraception for Women Aged Over 40 Years'*

Women <50 years of age - considered potentially fertile up to 2 years after her last menstrual period.

- A woman who is <50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill to provide both relief of menopausal symptoms and contraception
- It is recommended that the oral contraceptive is stopped at 50 years since there are more suitable alternatives.

Women > 50 years of age - considered potentially fertile up to 1 years after her last menstrual period[1]

Testosterone [3]

- Specialist advice should be sought before prescribing testosterone for this indication in primary care.
- Testosterone should only be offered as an option for improving low sexual desire when HRT is not effective.
- Testosterone currently does not have a UK marketing authorisation for this indication in women - the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.

C. Complementary therapies and unregulated preparations [1]

Herbal preparations, isoflavones and bioidentical hormones are not regulated by the European Medicines Authority and in some instances not subject to any quality control or research studies of sufficient power or quality.

- The efficacy and safety of unregulated compounded bioidentical hormones are unknown.
- Explain to women who wish to try complementary therapies that the quality, purity and constituents of products may be unknown.
- Advise women with a history of, or at high risk of, breast cancer that, although there is some evidence that St John's wort may be of benefit in the relief of vasomotor symptoms, there is uncertainty about:
  - Appropriate doses
  - Persistence of effect
  - Variation in the nature and potency of preparations
  - Potential serious interactions with other drugs (including tamoxifen, anticoagulants and anticonvulsants).[1]

D. Referral criteria [1, 3]

- Difficulty diagnosing menopause
- Contraindications to HRT
- Ineffectiveness of HRT - inadequate control/failure to respond despite logical changes in HRT
- Persistent side effects following logical therapy changes as per side effect management section
- Red flag symptoms e.g. unexplained bleeding
- Complex medical history
- Past history of hormone dependent cancer
- Bleeding problems
  - Sequential – increase in heaviness or duration of bleeding, or irregular bleeding
  - Continuous combined – bleeding beyond 6 months of therapy, or bleeding after a period of amenorrhoea

E. References

[1] British Menopause Society (online): HRT Guide. https://thebms.org.uk/_wprs/wp-content/uploads/2016/04/HRT-Guide-160516.pdf [Accessed on 13.02.2018]
[2] Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on [13.02.2018]
[3]National Institute for Health and Clinical Excellence (2015) Menopause: diagnosis and management. NICE guideline (NG23)
[4] Clinical Knowledge Summaries (online). Menopause (2015). <https://cks.nice.org.uk/menopause> [Accessed on 13.02.2018]

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Menopause and Hormone Replacement Therapy (HRT) Guidance and Treatment Pathway

TYPE OF HRT		OESTROGEN ONLY	SEQUENTIAL COMBINED	CONTINUOUS COMBINED
CRITERIA FOR USE		• Women without a uterus • Women with Mirena IUS in place Unopposed oestrogens cause endometrial proliferation: women with a uterus MUST have a progestogen to stop this	• Women with a uterus • Peri-menopausal: <12 months since last bleed or amenorrhoea	• Women with a uterus • Post-menopausal: >12 months since last bleed or amenorrhoea • >54 years • >1 year on sequential combined HRT
Rx CHARGE		1 prescription charge	2 prescription charges	1 prescription charge
ORAL	1st LINE	**Elleste Solo** Estradiol 1mg or 2mg	**Elleste Duet** Estradiol 1mg or 2mg & norethisterone 1mg	**Elleste Duet Conti** Estradiol 2mg & norethisterone 1mg
	2nd LINE	**Premarin** Conjugated oestrogen 0.625mg or 1.25mg	**If progestogenic side effects:** **Femoston 1/10 or 2/10** Estradiol 1mg or 2mg & dydrogesterone 10mg	**If progestogenic side effects:** **Femoston Conti** Estradiol 0.5mg or 1mg & dydrogesterone 2.5mg or 5mg
	3rd LINE	**N/A**	**N/A**	**Tibolone** See text for details
	ALTERNATIVES	**Bedol** Estradiol 2mg **Zumenon** Estradiol 1mg or 2mg **Progynova** Estradiol valerate 1mg or 2mg	**Clinorette** Estradiol 2mg, estradiol 2mg & norethisterone 1mg **Cyclo-progynova** Estradiol valerate 2mg & norgestrel 500mcg **Novofem** Estradiol 1mg & norethisterone 1mg **Tridestra** Estradiol valerate 2mg & medroxyprogesterone 20mg **Trisequens** Estradiol 1mg, estradiol 2mg, estradiol 2mg & norethisterone 1mg	**Kliovance** Estradiol 2mg & norethisterone 1mg **Kliofem** Estradiol 2mg & norethisterone 1mg **Angeliq** Estradiol 1mg & drospirenone 2mg **Indivina** Estradiol valerate 1mg or 2mg & medroxyprogesterone 2.5mg or 5mg **Premique low dose** Conjugated oestrogen 300mcg & medroxyprogesterone 1.5mg
TRANSDERMAL	1st LINE	**Evorel Patch** Estradiol 25, 50, 75 or 100mcg Change TWICE a week	**Evorel Sequi Patch** Estradiol 50mcg & norethisterone 170mcg Change TWICE a week	**Evorel Conti Patch** Estradiol 50mcg & norethisterone 170mcg Change TWICE a week
	2nd LINE	**If skin irritation with patch:** **Oestrogel** Oestradiol 0.06% gel 2 measures (1.5g oestradiol) daily	**If progestogenic side effects*:** **FemSeven Sequi Patch** Estradiol 50mcg & levonorgestrel 10mcg Change ONCE a week	**If progestogenic side effects*:** **FemSeven Conti Patch** Estradiol 50mcg & levonorgestrel 7mcg Change ONCE a week
	ALTERNATIVES	**Estradot** Estradiol 25, 37.5, 50, 75 or 100mcg **Estraderm MX** Estradiol 25, 50, 75 or 100mcg **Elleste Solo MX** Estradiol 40 or 80mcg **Progynova TS** Estradiol 40 or 80mcg	**NO ALTERNATIVES**	**NO ALTERNATIVES**
OLDER WOMEN (>60 years)*		**Premarin 300mcg** **Evorel 25 patch** **Oestrogel (1 measure)**	**N/A**	**Kliovance** Estradiol 1mg & norethisterone 0.5mg

VAGINAL ATROPHY

OVESTIN CREAM (estriol 0.1% vaginal cream) OR VAGIFEM (estradiol 10mcg vaginal tablet)

- OFFER to women with urogenital atrophy (including those on systemic HRT) and continue treatment for as long as needed to relieve symptoms
- CONSIDER for women with urogenital atrophy in whom systemic HRT is contraindicated
- Tablets and creams should be used nightly for two weeks and then twice weekly thereafter
- To be used with cyclical progestogen for at least 12 days of each cycle in women with a uterus
- The EMA's safety committee has recommended limiting the use of high-strength creams containing 100 micrograms/gram (0.01%) of estradiol to a single treatment period of up to 4 weeks.

*Older women may be less tolerant of oestrogen and need to start on a lower dose. See text for details.

ALTERNATIVE PRODUCTS MAY NEED TO BE USED DUE TO STOCK ISSUES. CONTACT YOUR PRACTICE SUPPORT PHARMACIST FOR FURTHER DETAILS.

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REVIEW	- At initiation of HRT or change in therapy - three months. - Established on HRT – at least annually. - Each review should assess effectiveness and side effects of therapy, discuss any bleeding pattern; review type and dose of HRT and help assess on-going risk/benefit balance.[3]
STOPPING HRT	- Treatment should be continued for as long as benefits of symptom control and quality of life outweigh risks. - Offer gradual reduction of HRT to limit recurrence of symptoms[1]
REFERRAL CRITERIA	- Contraindications to HRT - Ineffectiveness of HRT or on-going troublesome side effects - Red flag symptoms e.g. unexplained bleeding - Complex medical history or past history of hormone dependent cancer - Bleeding problems ○ **Sequential –** increase in heaviness or duration of bleeding, or irregular bleeding ○ **Continuous combined –** bleeding beyond 6 months of therapy, or bleeding after a period of amenorrhoea[2]