NENC ICB - Management of the Menopause

DIAGNOSIS[1,2]

The following can be diagnosed without laboratory tests in otherwise healthy women aged over 45 years with appropriate menopausal symptoms:

- Perimenopause - in woman with vasomotor and non-vasomotor symptoms (cognitive symptoms, mood disorders, sleep disturbance, fatigue, loss of libido, joint and muscle pain, headache, genitourinary symptoms) and changes in the menstrual cycle
- Menopause - in women who have had no period for at least 12 months and are not using hormonal contraception or with menopausal symptoms without a uterus. The average age for the menopause is 51.

These are the circumstances when Follicle-Stimulating Hormone (FSH) levels are required[2,3]:

- Age <40 years where premature ovarian insufficiency is suspected with elevated serum FSH levels (more than 30 IU/L) on two blood samples taken 4–6 weeks apart.

These are the circumstances when FSH levels may be required[2,3]:

- Age 40-45 years with menopausal symptoms and oligomenorrhoea or amenorrhoea
- Age >45 years exhibiting atypical symptoms (including anything other than classic menopausal symptoms)

Levels greater than 30 IU/L indicate a degree of ovarian insufficiency but not necessarily sterility. Isolated levels taken in the perimenopause can be misleading.

Restrict the measurement of serum FSH to support advice about stopping hormonal contraception in women **over 50** who have no periods. FSH can be measured in those using all progestogen only methods. Normal practice is to continue contraception until age 55 years.[3]

Information and advice[1,2]

Ensure patients (family or carers) are given information to include:

- Symptoms include irregular/cessation of periods, hot flushes, sweats, difficulty sleeping, aches and pains, vaginal dryness, mood changes/swings, anxiety, brain fog
- Explanation of the stages of the menopause
- Common symptoms and diagnosis
- Lifestyle changes and interventions to help general health and well being
- Benefits and risks of the treatments for menopausal symptoms (see page 4)
- Long term health implications of the menopause
- Contraception where required in those <55 years[3]
- Useful information for patients: menopause section on nhs.uk website or BMS Women's Health Concern website (www.womens-health-concern.org)
- Information on medicine shortages is available from SPS (www.sps.nhs.uk/home/tools/medicines-supply-tool/)

Address modifiable lifestyle factors to reduce menopausal symptoms[2,4]:

- Normalise weight with healthy balanced diet
- Consume adequate vitamin D (10mcg or 400 IU/day) and calcium (700mg/day). Useful information on the Royal Osteoporosis Society website look up 'calcium'
- Undertaking regular weight bearing exercise
- Advise/support women in smoking cessation
- Reduce alcohol intake
- Ensure other long-term conditions are managed appropriately
- Avoiding triggers for hot flushes if experiencing them (spicy foods, caffeine, alcohol etc.)
- Good sleep hygiene (Pzizz app, Sleepio app)
- Brain exercise (crosswords, sudoku), socializing, hobbies

Hormone Replacement Therapy (HRT)

Indications[1]:

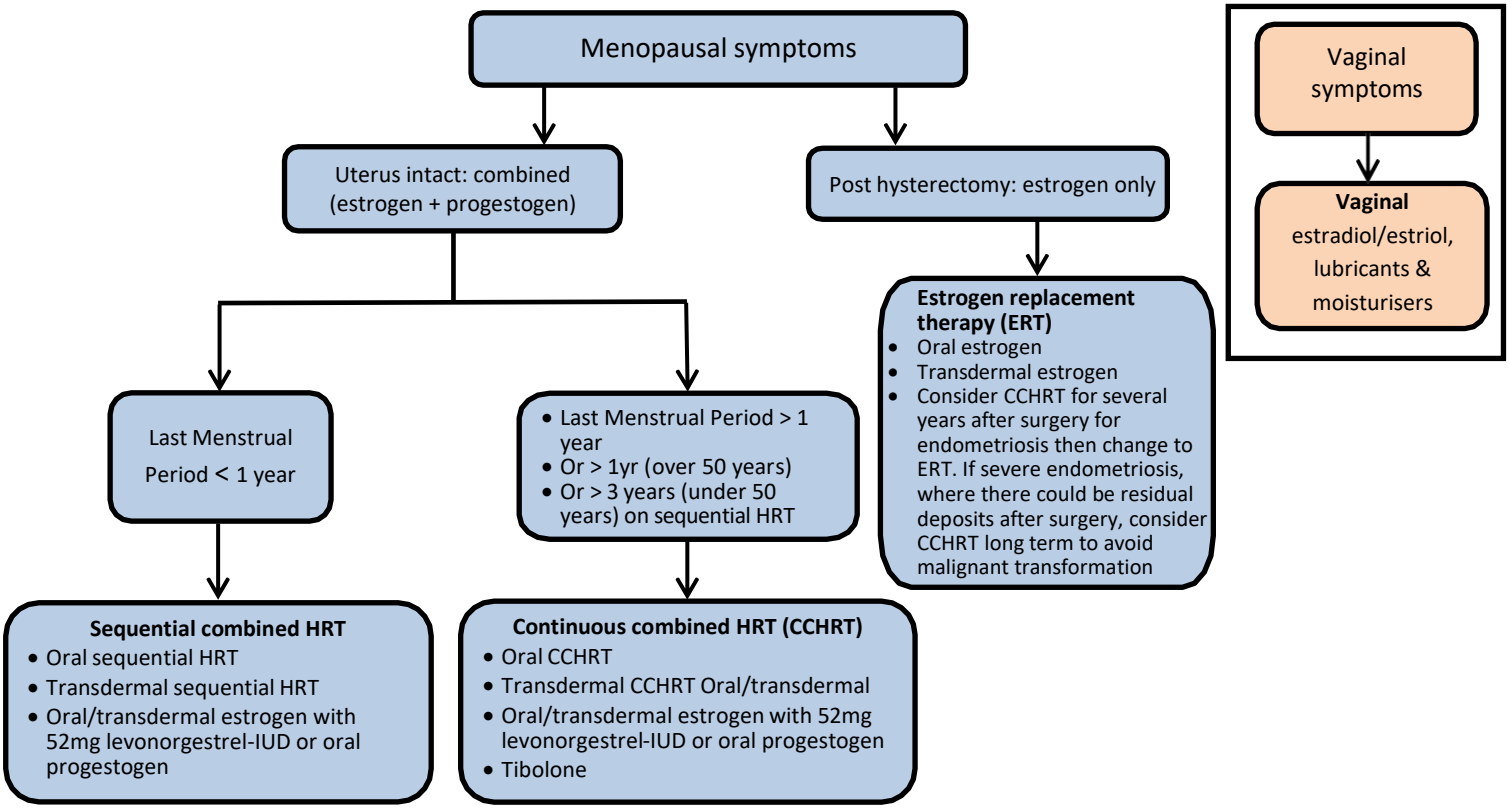
- Short term relief of hot flushes, night sweats
- Prevention of osteoporosis (long term) (see NENC ICB Osteoporosis guideline **LINK TO BE ADDED WHEN AVAILABLE**)
- Premature ovarian insufficiency (including surgical menopause)
- Relief of other menopausal symptoms e.g. sleep disturbance, anxiety/depression, and sexual function.
- HRT should not be prescribed solely for prevention of disease.

Contraindications[2]:

- Pregnancy
- Undiagnosed abnormal vaginal bleeding
- Active thromboembolic disorder or acute myocardial infarction
- Suspected or active breast or endometrial cancer
- Active liver disease with severely abnormal LFTs
- Caution with porphyria

Flow chart for Hormone Replacement Therapy (HRT) prescribing[1,2]

(Refer to table overleaf for formulary choices)



Prescribing considerations[2]

- HRT is available as oral or transdermal depending on patient preference and risk factors.
- Titrate up slowly according to symptoms and use the lowest effective dose to control symptoms.
- In women over 60 years, use lower HRT doses, either 0.5mg estradiol orally or transdermal estradiol +/- progestogen.
- Consider transdermal HRT in women with:
  *BMI >30 *poor control or side effects on oral HRT *controlled hypertension *hypertriglyceridaemia
  *history of, or risk of venous thromboembolism (VTE), consider referring to specialist for advice
  *history of, or risk of cardiovascular disease, consider referring to specialist for advice
  *bowel disorder which may affect absorption of oral therapy * history of migraine (benefit from steady hormonal levels)
  *taking interacting drugs (hepatic enzyme inducers) e.g. anticonvulsants *lactose sensitivity *history of gallstones

When to refer[2]:

- Persistent side effects despite changing HRT
- Inadequate control of menopause symptoms despite changes in HRT (e.g. titration of HRT dose or change to route of delivery)
- Complex medical history
- In women with hormone dependent tumours who have troublesome menopause symptoms
- Premature ovarian insufficiency (see separate box)
- Bleeding problems (refer to Newcastle, South Tyneside and Sunderland Approach to Gynaecological Problems in Primary Care **LINK TO BE ADDED WHEN AVAILABLE**)
  - during sequential HRT – if irregular bleeding continues after first 6 months, if there is a change in bleeding pattern after 6 months including increased duration, frequency and/or heaviness, irregular bleeding and associated pain
  - during CCHRT or tibolone – if bleeding continues after first 6 months or if bleeding occurs after 6 months of no bleeding

Premature ovarian insufficiency (POI)[2]

In POI (menopause < 40 years old) it is important to start treatment with either HRT or a combined hormonal contraceptive (CHC). Treatment should continue until the age of natural menopause (unless contraindicated) to protect against increased risks of dementia, cognitive decline, cardiovascular disease and osteoporosis.

Counsel women that:

- HRT has no effect on blood pressure and beneficial effects on metabolic parameters, when compared with CHC but is NOT a contraceptive
- Both HRT and CHC offer bone protection.

Refer all women with POI under age 35.
Consider referring women >35 and <40 with POI to a specialist for help and support in the physical and psychosocial aspects of their diagnosis.

HRT formulary

Clinicians can prescribe off formulary in the event of supply issues

Route of HRT is dependent on patient choice and risk factors	Type of HRT	Sequential combined HRT	Continuous combined HRT	Estrogen Replacement Therapy (ERT)	Progestogen (See box below for features)
	Criteria for use	➢ **Intact uterus** ➢ **Perimenopausal – had at least one natural period in last year**	➢ **Intact uterus – had no period for 1 year** ➢ **Over 50 and >1 year on sequential HRT or under 50 and > 3 years on sequential HRT**	➢ **Post hysterectomy** ➢ **Intact uterus - in combination with a separate progestogen preparation (see progestogen column)**	➢ **As adjunct to transdermal or oral estrogen if not had a hysterectomy**
ORAL	1st line	Elleste Duet tablets 1mg or 2mg estradiol & 1mg norethisterone	Elleste Duet Conti 2mg estradiol & 1mg norethisterone	Elleste Solo 1mg or 2mg estradiol	52 mg Levonorgestrel-IUD
	2nd line	Femoston 1/10 or 2/10 tablets 1mg or 2mg estradiol & 10mg dydrogesterone	Femoston Conti 0.5/2.5 = 0.5mg estradiol & 2.5mg dydrogesterone OR 1/5 = 1mg estradiol & 5mg dydrogesterone		Micronised Progesterone 100mg daily or200mg days 14-28
	3rd line		Tibolone 2.5mg tablets		Medroxyprogesterone acetate (Provera) 10mg days 14-28 or 5mg daily
TRANSDERMAL	1st line	Evorel Sequi patches 50micrograms estradiol & 170micrograms norethisterone Change patch TWICE a week	Evorel conti patch 50micrograms estradiol & 170micrograms norethisterone Change patch TWICE a week	Evorel/Estradot patch 25, 50, 75, 100mcg estradiol Change patch TWICE a week	**Testosterone supplementation** • Testogel sachet, 40.5mg/2.5g sachet, 1/8th sachet a day • Testim 50mg/5g tube, 1/10th tube a day • Tostran (2% testosterone gel in a canister containing 60g) starting dose 1 metered pump on alternate days
				Topical gels: option where skin irritation occurs with patch • Oestrogel: 0.06% estradiol gel, 1-4 measures (2.5g) estradiol daily • Lenzetto (1.53mg/spray), 1-3 sprays daily	

Monitoring[2]

Started on HRT or HRT changed— review at 3 months

Established on HRT—review annually unless thereare clinical indications for earlier review.

At each review, assess efficacy, side effects and ongoing risk/benefit balance.

Stopping HRT[2]

There is no arbitrary limit on HRT duration. In women with POI, HRT should be continued until normal menopause age. Withdraw HRT slowly to reduce risk of recurrent symptoms.

If symptoms do recur then recommence treatment.

Urogenital atrophy[2]

Ovestin cream (0.1% estriol vaginal cream) OR Vagirux (10 microgram vaginal tablet). Other lower dose preparations are available, see BNF.

- Use every night for 14 nights then twice weekly.
- Start early before irreversible changes have occurred. Can betaken with systemic HRT.
- If symptoms not relieved consider dose increase, after seeking advice from specialist.
- Explain that symptoms may come back when treatment is stopped, adverse effects are rare.
- Moisturisers and lubricants (**OTC purchase**) can be used alone or in addition to vaginal estrogen for vaginal dryness.
- Report any unscheduled bleeding promptly.

If preparation exists at lower dose reduce dose for 4 weeks then stop.If already on lowest dose or no lower strength exists then simply stop.

Progestogens (features)		
Synthetics		
C19	**Norethisterone, Norgestrel, Levonorgestrel**	Better cycle control, androgenic (may be good for libido). Unfavourable effect on lipids.
C21	**Medroxyprogesteroneacetate**	Can be added to oral or transdermal estrogen, mildly androgenic (may be good for libido). Unfavourable effect on lipids.
	Dydrogesterone	Non androgenic. Not available as single preparation.
	Levonorgestrel IUD 52mg	Replace after 5 years as per FSRH guidance. Provides bleed-free option for perimenopause
Body identical		
Micronised progesterone (Utrogestan)		Fewer progestogenic S/Es, no androgenic or glucocorticoid activity. No lipid effects. Less effective cycle control.

Benefits and risks of HRT

Benefits of HRT[1,2]	
➢ Reduction in vasomotor symptoms ➢ Improved sleep, joint pain & QOL ➢ Potential improvement in psychological symptoms e.g. depression & anxiety ➢ Relief of vaginal dryness ➢ Improved sexual function	➢ Reduced risk of coronary heart disease when estrogen is started early (within 10 years of menopause) ➢ Improved bone mineral density, reduced fracture risk

Managing side effects[2] Encourage women to persist with treatment for 3 months (as adverse effects may resolve)	
Estrogen-related	**Progestogen-related**
Fluid retention, bloating, breast tenderness or enlargement, nausea, headaches, leg cramps, and dyspepsia. They may occur continuously or randomly throughout the cycle.	Fluid retention, breast tenderness, headaches or migraine, mood swings, depression (similar to PMS), acne. They tend to occur in a cyclical pattern during the progestogen phase of sequential HRT).
Management strategies	
◦ Change route of delivery. ◦ Dose reduction. ◦ Leg cramps may improve with lifestyle changes e.g. exercise, stretching calf muscles. ◦ Nausea – switch to transdermal or adjust the timing of the estrogen dose, or take with food. ◦ Breast tenderness may be alleviated by a low-fat diet. ◦ Migraine – consider starting at low dose and titrate up gradually, and consider transdermal rather than oral HRT preparations.	◦ Changing the progestogen type (see 'Progestogen features' table on page 3). ◦ Change route of delivery. ◦ Reducing the regimen of progestogen administration. Progestogens can be taken for 10–14 days of each monthly sequential regimen, so swapping from a 14-day to a 10-day product may provide benefit. ◦ Changing to continuous combined therapy or tibolone often reduces progestogenic adverse effects with established use. However, this option is only suitable for postmenopausal women. ◦ Reducing the frequency of progestogen dosing by prescribing Tridestra (91 tablets with 2mg estradiol valerate for 70 days, 2mg estradiol valerate and 20mg medroxyprogesterone acetate for 14 days then placebo for 7 days). Long cycle HRT may increase endometrial hyperplasia over time therefore it is advisable to convert patients to a CCHRT regimen as soon as it is practical.

Cardiovascular and cerebrovascular disease[1,2]
- There is a reduced risk of coronary heart disease when estrogen is started early (within 10 years of menopause).
- HRT does not increase coronary heart disease (CHD) risk when started in women aged under 60 years old, and does not affect the risk of dying from cardiovascular disease.
- CVD co-morbidities are not a contra-indication to HRT as long as they are optimally managed.
- ERT is associated with no increased risk of CHD.
- Transdermal combined HRT is associated with no increased risk of CHD.
- Oral estrogen is associated with a small increase in risk of stroke. As the baseline risk of stroke in women under 60 years is very low, the increased risk is small (1 extra woman per 1000 using HRT).
- In women with past history of CVA or TIA, discuss with local specialist.

Venous thromboembolism (VTE)[2]
- Risk is increased 2-fold with oral HRT compared to baseline population risk.
- No increased risk with transdermal HRT given at standard therapeutic doses (under 50mcg/24hr) compared to baseline population risk.
- Consider transdermal rather than oral HRT in women with an increased risk of VTE, e.g. BMI over 30.

Type 2 diabetes[2]
- There is no increased risk of developing type 2 diabetes with any type of HRT.
- HRT is not associated with an adverse effect on blood glucose control in diabetics.

Osteoporosis[2]
- Give women advice on bone health and discuss any risk factors for osteoporosis.
- Risk of fragility fractures is decreased whilst taking HRT but increases once treatment is stopped, and the benefit varies depending on the length of HRT use.

Loss of muscle mass and strength[2]
- Limited evidence suggests HRT improves muscle mass or strength, which normally decreases after the menopause. Muscle mass/strength is maintained through weight bearing exercise and where relevant smoking cessation and avoiding excessive alcohol intake should be advised.

Breast cancer[1,2]
- All types of ERT associated with a small increased risk of breast cancer (extra 3 per 1000 taking ERT for 5 years in 50s).
- Combined HRT is associated with an increased risk of breast cancer (8 extra cases per 1000 taking HRT for 5 years in their 50s) and reduces back to background rate after 5 years.
- In women who have had breast cancer, non-hormonal options should be discussed. Local vaginal estrogen is an option in those taking tamoxifen if moisturisers/lubricants produce no relief.

Ovarian cancer[1,2]
- ERT or HRT has little effect on the incidence of ovarian cancer (1 extra case per 1000 taking HRT in their 50s).

Non-hormonal options[2]

- Limited evidence to support use of 'over the counter' remedies.
- Evidence suggests that the following may be helpful:
  - Clonidine slowly increased from 25mcg twice a day for 2 weeks to a maximum dose of 50mcg three times a day. Side effects include dizziness, dry mouth and constipation. Do not stop suddenly as this can cause rebound hypertension.
  - Venlafaxine 37.5mg slowly increased up to 150mg a day, Paroxetine 10mg or Citalopram 10mg-30mg a day, side effects include dry mouth, constipation, and nausea are more likely with higher doses.

Testosterone supplementation[5]

- Patients should be taking systemic HRT for menopausal symptoms and be suffering from loss of libido.
- Other androgen deficiency symptoms include lethargy, loss of muscle mass and strength, lack of motivation, low wellbeing and lowered mood (all non-specific with no RCT evidence showing an improvement with testosterone). More common in women with POI, over 60 and where both ovaries have been removed.
- Adequately treat symptoms of vulvovaginal atrophy before testosterone is considered.
- Consider psychosexual counselling.
- Consider tibolone, which has some androgenic properties.
- BMS guidance on testosterone replacement in menopause can be found here: www.thebms.org.uk/wp-content/uploads/2022/12/08-BMS-TfC-Testosterone-replacement-in-menopause-DEC2022-A.pdf

Prescribing testosterone:

- A blood test is required before prescribing testosterone. Serum total testosterone levels should be checked to establish a baseline for future monitoring and to ensure that levels are not outside the normal range before treatment is commenced.
- Testosterone supplementation should not be prescribed in women with a serum testosterone >1.4nmol/L.
- Testosterone takes 10-12 weeks before benefit is felt.
- Treatment should be trialed for a minimum of 3 months and maximally for 6 months before being discontinued if there is lack of efficacy.
- Duration of use should be individualised and evaluated at least on an annual basis, weighing up risks and benefits. Currently there are no long-term safety data of using testosterone supplementation in women.
- Testosterone products are off-label/license for female usage.

Monitoring testosterone supplementation:

- At three months, serum testosterone should be repeated aiming for levels of 0.5 to 2.4 nmol/L.
- Monitoring continues every 6-12 months to ensure that levels remain within the female physiological range in order to minimise adverse effects.

How to use testosterone products:

Testosterone gel should be applied to clean dry skin (upper thighs) and allowed to dry before dressing (takes 5-8mins). Skin contact with partners or children should be avoided until dry. Hands should be washed immediately after application. The area of application should not be washed for 2-3 hours after application. The site of gel application on the thigh should change each day to avoid the small risk of localised hair growth.

Side effects of testosterone supplementation:

- If testosterone levels are maintained within the female physiological range side effects are rare. Side effects include excess hair growth, acne and weight gain which are usually reversible with reduction in dosage or discontinuation.
- Alopecia, deepening of voice and clitoral enlargement are rare with physiological testosterone replacement.

Title	NENC ICB – Management of the Menopause
References	1. NICE guidelines [NG23] Menopause: diagnosis and management, last revised December 2019 https://www.nice.org.uk/guidance/ng23 2. NICE Clinical Knowledge Summaries Menopause, last revised March 2022 http://cks.nice.org.uk/menopause 3. FSRH Clinical Guideline: Contraception for women aged over 40 years, amended September 2019 https://www.fsrh.org/documents/fsrh-guidance-contraception-for-women-aged-over-40-years-2017/ 4. NICE Guidelines Vitamin D deficiency in adults, last revised January 2022 https://cks.nice.org.uk/topics/vitamin-d-deficiency-in-adults/management/prevention/ 5. British Menopause Society Guidelines Testosterone replacement in menopause https://thebms.org.uk/publications/tools-for-clinicians/testosterone-replacement-in-menopause/ 6. Menopause matters guidelines. Hormone replacement therapy. https://www.guidelines.co.uk/menopause-matters/hrt
Authors	With thanks to Dr Imogen Shaw, GPwSI in Mid-Essex Clinical Commissioning Group Adapted by Tyne and Wear Menopause Group: Dr Diana Mansour, Consultant in Community Gynaecology, The Newcastle upon Tyne Hospitals NHS Foundation Trust Dr Kathryn Clement, Consultant in Sexual and Reproductive Healthcare, The Newcastle upon Tyne Hospitals NHS Foundation Trust Dr Sarah-Jane Gatiss, Consultant in Obstetrics and Gynaecology, South Tyneside and Sunderland NHS Foundation Trust Dr Katherine Gilmore, Consultant in CSRH, South Tyneside and Sunderland NHS Foundation Trust Dr Kaia Scurr, Specialty Trainee in CSRH, The Newcastle upon Tyne Hospitals NHS Foundation Trust Dr Rachael Viney, Specialty Trainee in CSRH, South Tyneside and Sunderland NHS Foundation Trust Dr Alice Townsend, Specialty Trainee in CSRH, South Tyneside and Sunderland NHS Foundation Trust
Approved by	NENC Medicines Subcommittee
Date approved	17.10.2023
Next review date	17.10.2026