# The menopause and the use of hormone replacement therapy (HRT)

**This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and/or carer. Health care professionals must be prepared to justify any deviation from this guidance.**

## INTRODUCTION

This guideline aims to offer a clear but comprehensive plan for the management of menopausal symptoms including:

- HRT use in the post-menopause
- HRT use in the peri-menopause
- HRT use in early menopause

The guideline discusses how to assess a patient, identify risks which will alter management, and how to counsel a patient appropriately. Contraindications to HRT use are explained, strategies for commencing therapy discussed, and strategies to overcome irregular bleeding.

This guideline should be used in conjunction with the most up to date version of the British National Formulary

## THIS GUIDELINE IS FOR USE BY THE FOLLOWING STAFF GROUPS:

Medical staff

**Lead Clinician(s)**

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This is the most current document and should be used until a revised version is in place

**Key amendments to this guideline**

| Date | Amendment | By: |
|---|---|---|
| 01/08/18 | Complete Guide on management of Menopause | Mr SC Agwu.<br>Dr M Yosef |
| Dec 2020 | Document approved for 3 years | Miss Alex Blackwell |

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| Dec 2023 | Document extended for 6 months whilst under review | Alex Blackwell |
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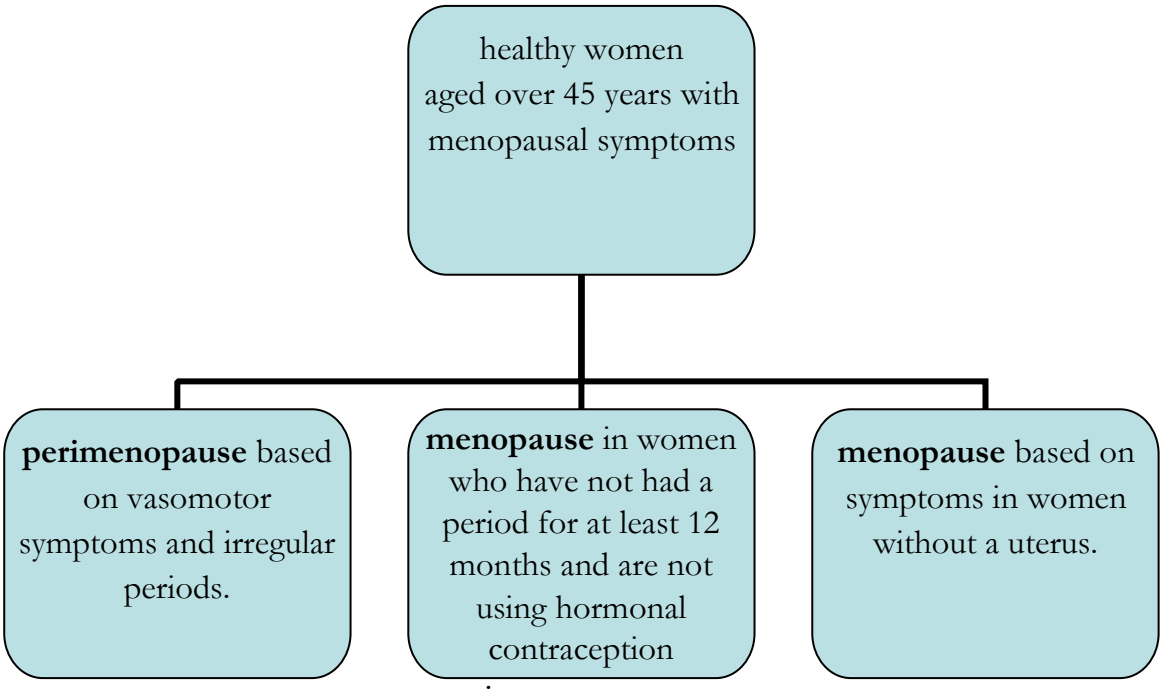
# The menopause and the use of hormone replacement therapy

## *Introduction:*

- 80% of women will develop menopausal symptoms, however only 10% have symptoms severe enough for them to consultant healthcare providers. Symptom duration varies from around 3 months to 5 years.
- 70% of women will experience vasomotor symptoms such as hot flushes or night sweats. Some women also report psychological or physical symptoms, including tiredness, insomnia, low mood, memory problems, mood swings, loss of libido, joint pains or vaginal dryness.
- The average age of the menopause in the UK is 52 years.
- Women in the UK can expect more than 30 years of postmenopausal life (based on current average life expectancy of 81 years).

## Diagnosis of the Menopause :



FSH levels may be useful in diagnosing the menopause in patients under 45 years with atypical symptoms.

- If FSH, LH or oestradiol levels are measured , samples should be taken on two occasions 6 to 8 weeks apart. If the woman is not amenorrhoeic the first sample should ideally be taken in the first 5 days of the cycle.
- FSH level over 30 IU/L is diagnostic of ovarian decline. Fluctuations of FSH in perimenopause limit its value. FSH should not be done if taking combined oestrogen and progestogen contraception or high dose progestogen.

## *Indications for HRT use :*

- Consider HRT to manage menopause symptoms including vasomotor symptoms, psychological symptoms (including low mood that arises as result of menopause), altered sexual function and urogenital atrophy.
- In women with premature ovarian insufficiency (premature menopause), systemic HRT is recommended, if not contraindicated, until at least the average age of natural menopause (51-52 years) to prevent the early onset of osteoporosis, CVD, Alzheimer's disease, Parkinsonism and cognitive decline.
- HRT may be appropriate for prevention of osteoporosis related fractures in women below the age of 60 years or within 10 years of menopause in symptomatic women or if other bone protection medication is contraindicated.

## *Assessment of women before starting HRT :*

1. History of menopause and other symptoms , Menstrual history ,Contraceptive needs (HRT is not contraceptive)

2. Obtain a personal and family medical history. Assess risks of:
   - cancer—breast, bowel, ovarian
   - osteoporosis
   - venous thromboembolism
   - CV risks

3. Check patient up to date with their cervical smears and mammograms if indicated. 4.

   Check blood pressure, height, weight, BMI

Modifiable lifestyle factors - ensure that these are addressed:

1. Women should be advised to eat a healthy balanced diet, to maintain a healthy BMI, to ensure they eat sufficient dietary calcium (700mg/day) and undertake regular weight-bearing exercise.
2. Ensure that a discussion occurs with the patient in order to address stopping smoking, reducing alcohol intake.
3. Ensure optimum treatment of conditions such as diabetes and blood pressure as applicable in order to reduce the impact of such diseases on menopausal symptoms.

## *Counselling women regarding HRT*

To allow a patient to make an informed decision on their ongoing management a discussion with them should include:

- The benefits and risks of systemic HRT, individualised to the patients individual circumstances.
- Alternative therapies to systemic HRT
- Discuss the use of vaginal oestrogens where appropriate

## *Benefits of HRT*

- Reduction of vasomotor symptoms.
- Relief of vaginal dryness and improved sexual function.
- Improved sleep, joint pain and quality of life. Improved bone mineral density and reduced fracture risk.
- HRT may improve psychological symptoms e.g. depression and anxiety.
- Other possible benefits include the reduction in risk of colonic cancer, dementia/Alzheimers, prevention of diabetes, macular degeneration and cataract formation, with improved dentition and skin healing – these are still controversial and not seen as indications.

## *Risks of HRT*

- The risks associated with HRT use for early menopause (<50) is no different than healthy subjects

- In most patients who commence HRT for symptom control at the time of the peri-menopause and early menopause (age 50-59) the benefits on quality of life outweigh the small increase in risks. These risks are summarised in table 1.
- The risks of HRT use increase after use longer than 5 years, and in patients over the age of 60. The increased risk in these situations needs to be weighed against the benefits of continuing HRT use.

**TABLE 1: 5 year incidence rates for women aged 50-59 using systemic HRT**

| Risk | Background 5 year incidence per 1000 women not on HRT aged 50-59 | Additional cases per 1000 women on oestrogen only HRT for 5 years | Additional cases per 1000 women on combined HRT for 5 years |
|---|---|---|---|
| Breast cancer | 10 | 2 | 6 |
| Ovarian cancer | 2 | 1 | 1 |
| Endometrial cancer* | 2 | 4 | 0 |
| VTE** | 5 | 2 | 7 |
| Stroke | 4 | 1 | 1 |

Research is ongoing into the effects of HRT on coronary heart disease. In women aged 50-59 it is likely that HRT either has no effect or possibly protect against heart disease. The risk increases in women who have used HRT for longer than 10 years after the menopause.
When HRT is stopped the excess risk of breast and ovarian cancer disappears after 5 years. The risk of VTE soon after discontinuing HRT.

## *Contraindications*

- Current, past, or suspected breast cancer, Known or suspected oestrogen-sensitive cancer.
- Undiagnosed abnormal vaginal bleeding ,Untreated endometrial hyperplasia.
- Current venous thromboembolism (deep vein thrombosis or pulmonary embolism), unless the woman continues on anticoagulant treatment.
- Active or recent arterial thromboembolic disease (for example angina or myocardial infarction).
- Untreated hypertension.
- Active liver disease with abnormal liver function tests , Dubin-Johnson and Rotor syndromes (or monitor closely) .

## *Cautions for HRT use*

- A personal or first degree relative with any history of venous thromboembolism (whether provoked or unprovoked)
- Migraines (transdermal preparation starting low dose is advised with dose gradually increased to control symptoms without exacerbating migraines.

## *Prescribing HRT to minimise the risks:*

- The lowest dose of oestrogen required to adequately reduce symptoms should be used
- The regimen, dose of HRT and the duration of treatment should be individualised, and the risks and benefits should be reviewed on annual basis.
- HRT should only be used while needed to control a patient's symptoms , and it is advisable to stop HRT after two years to see if symptoms have settled.
- Similarly to hormonal contraception HRT should be stopped four weeks prior to any planned surgery to limit the risk of post-operative VTE.

## *Choice of route*

Offer patient choice of oral or transdermal. Avoid oral if

- VTE risks or personal /first degree relative with history of VTE (both provoked and unprovoked)
- Poor symptom control with oral.
- Bowel disorder /absorption problems /gastric banding, • History of migraines.
- Stroke risks e.g. BMI>30/smoker/sedentary.
- History of or concerns of gall stones.
- On hepatic enzyme inducing agent .

## *Prescribing options for HRT*

Systemic HRT reduces symptom severity and frequency by 80-90%. It takes a couple of weeks to start to improve the symptoms of hot flushes and night sweats, and takes a couple of months to improve vaginal symptoms.

- Oestrogen only HRT
  - Oestrogen should only be used alone when a hysterectomy has been performed.
  - The Mirena IUS is licensed for four years as the progesterone part of combined HRT. If a mirena is in situ then oestrogen only HRT can be used.

- Continuous combined HRT
  - Oestrogen and progesterone at the same doses every day.
  - Used in postmenopausal women who have a uterus but have not had a period for over 1 year. ○ If used in peri-menopausal patients it is likely to cause breakthrough vaginal bleeding.

- Sequential combined HRT
  - Oestrogen dose is the same every day providing symptom relief.
  - Progesterone is contained in the medication for 12-14 days a month.

- This causes withdrawal bleeding every month.
- It is used in women who are peri-menopausal/ not one year since their last period.
- By allowing a withdrawal bleed it reduces the risk of unpredictable breakthrough bleeding.
- A patient can be switched to continuous combined after 12 months if over 50.

- Tibolone
  - This is a synthetic steroid compound ( selective estrogen receptor modulator ) it has oestrogenic, progestogenic and androgenic actions.
  - It conserves bone mass and treats vasomotor, psychological and libido problems (due to its androgenic effects).
  - There is an increased risk of breast cancer and venous thromboembolism, broadly similar to combined HRT. Its use in women over 65 years needs to be cautious because of increased stroke risk. ○ Often used as add back therapy to patients using GnRH analogues for treatment of endometriosis.

- Topical estrogen
  - First line therapy for women with vaginal atrophy ○ Can be used in conjunction with systemic HRT
  - May be used in women for whom systemic HRT is contraindicated following advice from a clinician with expertise in menopause management
  - It should be continued for as long as needed to manage symptoms as these will return once the preparation is stopped
  - Topical estrogen cream, pessaries and vaginal rings are all equally effective
  - Vaginal administration results in minimal systemic absorption and therefore very few side effects
  - Women should be advised to attend for review if they experience any unscheduled vaginal bleeding

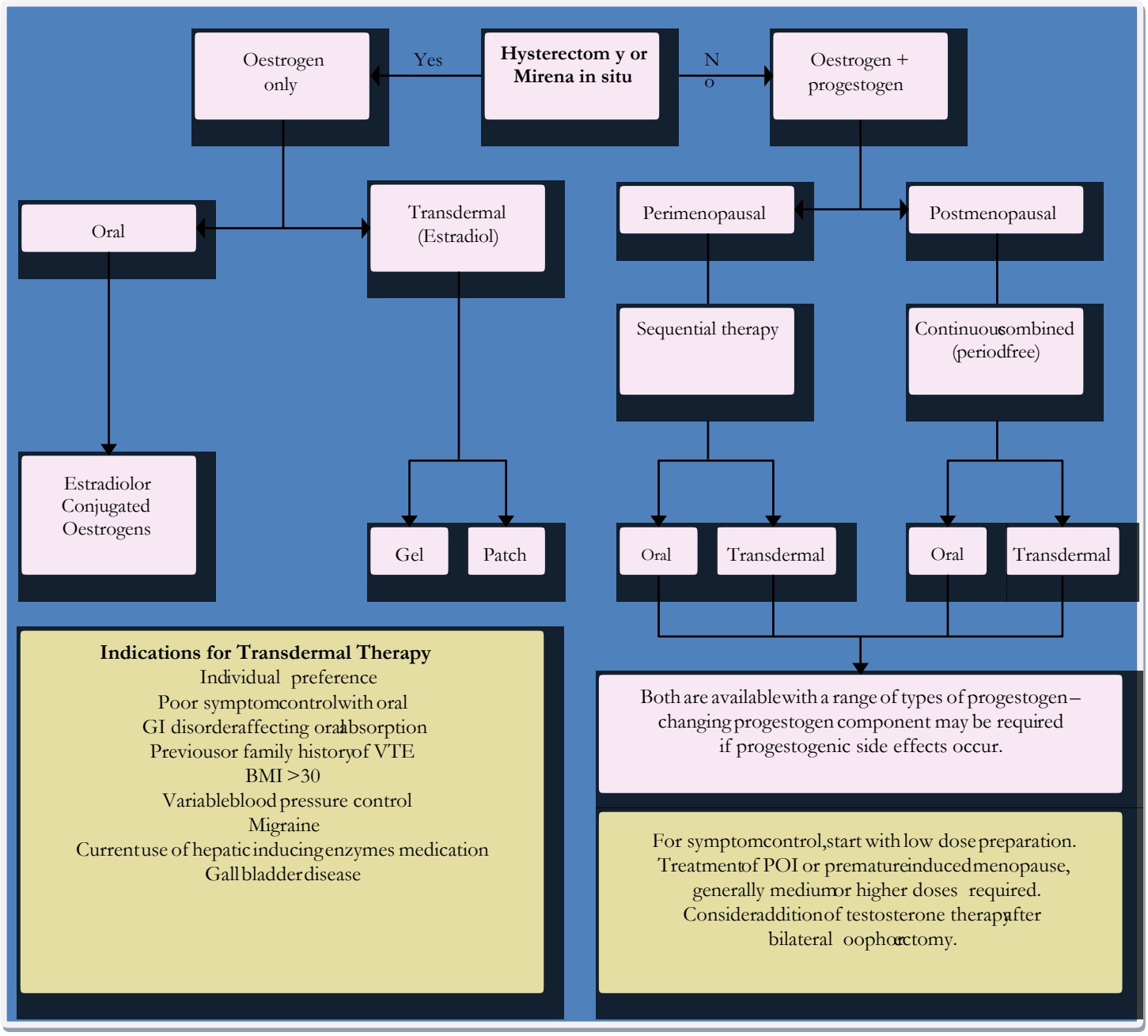
- Testosterone
  - In studies testosterone supplementation may help improve libido in women who have undergone bilateral oophorectomy. NICE recommend testosterone supplementation for menopausal women with low sexual desire when HRT alone is not effective.
  - At present, there is no licensed product for women as testosterone patches and implants have been withdrawn for commercial reasons.
  - Before initiating the treatment :

    ✦ Investigate other causes of low libido and if necessary treat first. Testosterone should only be prescribed if libido continues

to remain low and where there is no other obvious cause of low libido.

- Carry out blood tests to check sex hormone binding globulin (SHBG) and testosterone to show that FAI (free androgen index) is within the normal range before treatment is started.
- Ensure that women are on oestrogen HRT before and while taking testosterone.
- Testosterone levels should be kept between 1-2 nmol/L.

- An 'off-label' testosterone gel option is using one sachet or tube of gel over 7-10 days (Testogel 50mg/5g sachet or Testim 50mg/5g tube).
- Administered by the patient herself, onto clean, dry, healthy skin on the sites indicated by the manufacturer. Applied immediately onto the skin. Allow drying for at least 3-5 minutes. before dressing. Wash hands with soap and water after applications.
- Usually treatment takes up to 3 months to be effective, so a 3 month follow up should be arranged and then 3 monthly follow up appointments continue until a woman is established on treatment. Recheck the free androgen index (FAI) if testosterone side effects occur.



**Adjunctive progestogen in HRT—**use alongside either oral or transdermal oestrogen for women with uterus to provide endometrial protection.

**Intrauterine system (Mirena) -** NB Licensed for 4 years for HRT use
**Medroxyprogesterone acetate (provera) tablets**
cyclical regime—10mg for 12 days each 28 day cycle
continuous combined HRT—2.5-5mg daily continuously
**Utrogestan (micronized progesterone) capsules**
Cyclical regime—200mg orally at bedtime for 12 days each 28 day cycle
Continuous combined HRT—100mg orally daily continuously at bedtime

**Oestrogen only**

H sterectomy, 1 prescription charge

| HRT Product | Oestrogen | Delivery | Dose | Indication for use |
|---|---|---|---|---|
| Elleste solo | Oestradiol | Oral tablets | 1 mg, 2mg daily | First line oral treatment option |
| Premarin | Conjugated equine oestrogen | Oral tablets | 300mcg, 0.625mg, 1.25mg daily | Consider if previously well on conjugated equine oestrogen. |
| Evorel | Oestradiol | Transdermal patches | 25,50,75,100 mcg twice weekly | First line transdermal option |
| Elleste Solo Mx | Oestradiol | Transdermal patches | 40, 80mcg twice weekly | Skin allergy /poor absorption with Evorel, alternative adhesives |
| Estradot | Oestradiol | Transdermal patches | 25, 37.5, 50, 75, 100mcg twice weekly | Smaller sized patches consider for higher doses and petite women |
| Sandrena | Oestradiol | Transdermal gel | 0.5, 1, 1.5 mg/g daily | Patient preference, skin allergy to patches or side effects |

**Sequential/cyclical combined HRT**

**Uterus present, perimenopausal women, 2 prescription charges, monthly bleed**

| HRT Product | Oestrogen/progestogen | Delivery | Dose Oestrogen/ progestogen | Indication for use |
|---|---|---|---|---|
| Elleste duet | Oestradiol /norethisterone | Oral tablets | 1mg/1mg 2mg/1mg daily | First line oral treatment option |
| Femoston | Oestradiol/dydrogesterone | Oral tablets | 1mg/10mg 2mg/10mg daily | If cyclical side effects to norethisterone or other progestogen |

| | | | | |
|---|---|---|---|---|
| Prempak C | Conjugated equine oestrogen/norgestrel | Oral tablets | 0.625mg/150mcg 1.25mg/150mcg daily | Consider if previously well on conjugated equine oestrogen. |
| Evorel Sequi | Oestradiol/norethisterone | Transdermal patches | 50mcg/170mcg twice weekly | First line transdermal treatment option |
| FemSeven Sequi | Oestradiol/levonorgestrel | Transdermal patches | 50mcg/10mcg once weekly | Skin allergy /poor absorption with Evorel, alternative adhesives |
| Oestradiol tablet/ patch/gel as above plus adjunctive progestogen/ progesterone | Oestradiol plus proges-togen/progesterone of choice (see table below) | | | Side effects with other progestogens, bleeding problems, contraceptive needs |

**Continuous combined HRT**

Uterus present, postmenopausal women, 1 prescription charge, cycle free

| HRT Product | Oestrogen/progestogen | Delivery | Dose Oestrogen/ progestogen | Indications for use |
|---|---|---|---|---|
| Kliovance | Oestradiol/norethisterone | Oral tablets | 1mg/0.5mg | First line oral treatment option |
| Femoston Conti | Oestradiol/dydrogesterone | Oral tablets | 1mg/5mg 0.5mg/2.5mg | If side effects to other progesto-gen |
| Premique low dose | Conjugated equine oes-trogen/ medroxyprogesterone acetate | Oral tablets | 0.3mg/1.5mg | Consider if previously well on con-jugated equine oestrogen. |
| Indivina | Oestradiol/ Medroxyprogesterone ace-tate | Oral tablets | 1mg/5mg | Continued irregular bleeding with other oral continuous combined HRT with no uterine pathology |
| Angeliq | Oestradiol/drospirenone | Oral tablets | 1mg/2mg | Bloating, breast tenderness, acne with other progestogens |
| Tibolone | Tibolone (synthetic molecule with oestrogen, progestogen and androgenic properties) | Oral tablets | 2.5mg | Low libido (also consider post hys-terectomy and/or BSO if libido low) |
| Evorel Conti | Oestradiol/norethisterone | Transdermal patches | 50mcg/170mcg twice weekly | First line transdermal treatment option |
| FemSeven Conti | Oestradiol/levonorgestrel | Transdermal patches | 50mcg/10mcg once weekly | Skin allergy /poor absorption with Evorel, alternative adhesives |
| Oestradiol only tablet/ patch/gel (see page 1) plus adjunctive proges- | Oestradiol plus progestogen/ progesterone of choice (see table below) | | | Side effects with other progesto-gens or bleeding problems |
| togen/progesterone Duavive | Conjugated oestrogens and | Oral tablets | 0.45mg/20mg | Amber continuation. Specialist |

bazedoxifene initiation only. If intolerant to pro-

**Topical vaginal oestrogen**

| HRT product | Oestrogen | Delivery | Dose | Indications for use |
|---|---|---|---|---|
| Vagifem | Oestradiol | Vaginal tablet | 10mcg as directed | First line topical treatment option |
| Gynest/Estriol 0.01% | Oestriol | Vaginal cream | Using applicator as directed | Patient or clinician preference |
| Estring | Oestradiol | Vaginal ring | 7.5mcg daily over 90 days | Allergies to other topical products, dexterity problems with applicators, patient preference |

## *Vaginal bleeding with HRT*

Those women with irregular vaginal bleeding taking HRT should be asked about:

- HRT compliance.
- HRT absorption e.g. diarrhoea or vomiting.
- Drug interactions e.g. liver enzyme inducing agents.

In the following situations further investigations are required and referral should be considered however, HRT does not needed to be stopped:

- Heavy, prolonged or irregular bleeding in sequential HRT users
- Bleeding associated with pain in sequential HRT users
- Heavy bleeding after previous light bleeding in sequential HRT users
- If irregular bleeding persists for more than the first 6 months in long cycle users (2 quarterly cycles)
- Continued vaginal bleeding after six months in users of continuous combined HRT
- If vaginal bleeding occurs after 6 months or more of amenorrhoea in users of continuous combined HRT

Immediate referral is advised in women with any of the above who are at increased risk of endometrial hyperplasia/endometrial carcinoma e.g. taking tamoxifen, those who are obese or diabetic.

A pelvic examination should be performed and the method of investigation depends on clinical assessment but should include a transvaginal ultrasound and when indicated a hysteroscopy/endometrial biopsy.

### *Alternatives to systemic HRT*

Clonidine 75 microgram twice daily:

- licensed to reduce vasomotor symptoms but generally ineffective.
- Decreases hot flushes in women on tamoxifen.
- produces marginal benefits over placebo in post-menopausal women.
- Dose should be increased slowly and follow up arranged.
- Gives troublesome side-effects for some women such as dry mouth, constipation, drowsiness and dizziness.
- May interact with antihypertensives.

Certain antidepressants have been shown to help vasomotor symptoms but their use is 'off- label':

- SSRIs and SNRIs may be effective in reducing hot flushes.
- Fluoxetine (20mg) reduces hot flushes by 60%.
- There is no evidence that SSRI or SNRIs alleviate low mood in menopausal women in the absence of a diagnosis of depression.
- Venlafaxine (37.5mg, 75mg or 150mg) has been shown to reduce hot flushes by 37%, 61% and 61% compared to 27% reduction for placebo. Usual starting dose is 37.5mg daily with gradual increase to reduce side effects such as nausea, dry mouth, insomnia, agitation and confusion.
- symptoms should respond within 2 weeks of commencing treatment.
- There are no long term studies to show that a reduction in vasomotor symptoms is maintained.

SSRI, SNRI and clonidine should not be routinely used first line for vasomotor symptoms, unless there are contraindications to hormonal replacement. SSRIs paroxetine and fluoxetine **should not be used** in women taking tamoxifen.

Gabapentin 900mg daily:

- has been shown against placebo to reduce hot flushes by 42-73%
- its use is 'off-label'
- adverse effects include drowsiness, arthralgia, weight increase, unsteadiness and dizziness side-effects may be reduced by gradual increase in dose.

### *Contraception, IUS and HRT*

- HRT is not contraceptive and will not prevent spontaneous ovulation in perimenopausal women.
- Women >50 years, use contraception for 1 year after last spontaneous period.
- Women <50 years, continue contraception for 2 years following last spontaneous period.
- Fit, healthy, non-smoking, normotensive women may continue the COCP until 50 years. The POP can be used alongside cyclical HRT.
- Barrier methods become safer in older women as fertility declines, and have a lower failure rate.
- The intra-uterine system (IUS) can be used as the progestogen component of HRT alongside oestrogen to provide contraception, control perimenopausal bleeding problems and provide endometrial protection.

### *Discontinuation*

- If a woman wishes to discontinue the dose can be reduced slowly over a 4-6 month period or stopped immediately. Gradual reduction may minimise the chance of symptom recurrence in the short term but makes no difference to symptoms in the longer term.
- If menopausal symptoms persist or return, after counselling, prescribe a low dose HRT , Often this lower dose will control menopausal symptoms with fewer side-effects.

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