Menopause and Hormone Replacement Therapy
Full Clinical Guideline

Reference No.: UHDB/Gynae/11:22/M2

Contents

1. Introduction

The menopause transition can have a considerable impact on many women. The majority of women will experience menopausal symptoms, and for a significant proportion troublesome symptoms may continue long-term. Hormone replacement therapy (HRT) is the most commonly used treatment for managing menopausal symptoms and has been shown to be the most effective intervention in this context.

All women should be able to access advice on how they can optimise their menopause transition and the years beyond. There should be a holistic and individualised approach to assessing and advising women, with particular reference to lifestyle advice and dietary modification. This should be an opportunity to discuss the advantages and disadvantages of the management options including HRT and non-hormonal therapies.

2. Scope and Purpose

This document aims to summarise the available evidence on management of the menopause and hormone replacement therapy. The guideline is based on two national guidelines: NICE Guideline 23: Menopause: diagnosis and management 2015 (1) and the British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women (2).

The guideline is intended to be used primarily by clinicians working within the menopause service and other secondary care clinicians seeing menopause patients. The guideline aids clinical judgement and does not replace it. In individual cases a healthcare professional may, after careful consideration, decide not to follow the guideline if it is deemed to be in the best interest of the woman.

3. Definitions

Androgen Deficiency Syndrome - lack of energy, reduced libido, headaches, muscle pain, joint stiffness and reduced metabolism. Caused by low serum testosterone. It frequently occurs after oophorectomy.

Body/Bio Identical Hormones are synthesised from plant phytoestrogens (soy or yams). Unlike synthetic hormones, micronised hormones allow for absorption in their natural form. The phrase body identical is the preferred term, where the hormone has been synthesised to be identical to endogenous hormones.

Compounded Bioidentical Hormones consist of unregulated plant-derived hormone combinations similar or identical to human hormones that are compounded by pharmacies to the specification of the prescriber. These products are unlicensed in the UK. The efficacy and safety of unregulated compounded bioidentical hormones are unknown.

Fragility fracture results from mechanical forces that would not ordinarily result in fracture (such as a fall from a standing height or less). Reduced bone density is a major risk factor for fragility fractures, which occur most commonly in the spine, hip and wrist.

Free Androgen Index (FAI) = total testosterone / SHBG x 100. Only active free testosterone is clinically significant.

Low mood - mild depressive symptoms that impair quality of life but are usually intermittent and often associated with hormonal fluctuations in the perimenopause.

Menopause - diagnose the following without laboratory tests in otherwise healthy women aged over 45 years with menopausal symptoms:

- perimenopause based on vasomotor symptoms and irregular periods
- menopause in women who have not had a period for at least 12 months and are not using hormonal contraception
- menopause based on symptoms in women without a uterus [2]

Perimenopause - the time in which a woman has irregular cycles of ovulation and menstruation leading up to the menopause and continuing until 12 months after her final period. The perimenopause is also known as the menopausal transition or climacteric.

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

Postmenopausal bleeding - vaginal bleeding that occurs after 12 months of amenorrhoea or 4 months after starting continuous combined HRT.

Urogenital atrophy - thinning and shrinking of the tissues of the vulva, vagina, urethra and bladder caused by oestrogen deficiency. This results in multiple symptoms such as vaginal dryness, vaginal irritation, urinary frequency and urinary tract infections.

Vasomotor symptoms - menopausal symptoms such as hot flushes and night sweats caused by constriction and dilatation of blood vessels in the skin that can lead to a sudden increase in blood flow to allow heat loss. These symptoms can have a major impact on activities of daily living.

4. Abbreviations

BMD	Bone Mineral Density
BMI	Body Mass Index
BMS	British Menopause Society
BP	Blood Pressure
BRCA	Breast Cancer gene
CBT	Cognitive Behavioural Therapy
cc-HRT	Continuous Combined HRT
CFS	Chronic Fatigue Syndrome
CHC	Combined Hormonal Contraceptive
CVD	Cardiovascular Disease
DXA	Dual Energy X-ray Absorptiometry
E2	Estradiol
EE	Ethinylestradiol
ER	Estrogen Receptor
FM	Fibromyalgia
FSH	Follicle Stimulating Hormone
GI	Glycaemic Index
GnRHa	Gonadotropin-Releasing Hormone agonist (GnRHa)
GP	General Practitioner
GPwSI	GP with Special Interest
GUM	Genito Urinary Medicine
HDL	High Density Lipoprotein
HPV	Human Papillomavirus
HRT	Hormone Replacement Therapy
HVS	High Vaginal Swab
IMB	Intermenstrual Bleeding
IMS	International Menopause Society
IUS	Intrauterine System
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LNG	Levonorgestrel
LH	Luteinising Hormone
LMP	Last Menstrual Period
MDT	Multidisciplinary Team
MPA	Medroxyprogesterone Acetate
MS	Multiple Sclerosis
NET	Norethisterone
PCOS	Polycystic Ovarian Syndrome
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
POI	Premature Ovarian Insufficiency
PR	Progesterone Receptor
PV	Per vagina
QOL	Quality of Life
RCT	Randomised Controlled Trial
RR	Relative Risk
SERM	Selective Estrogen Receptor Modulator
SHBG	Sex Hormone Binding Globulin
sc-HRT	Sequential Combined HRT
SNRI	Selective Noradrenaline Re-Uptake Inhibitor
SSRI	Selective Serotonin Re-Uptake Inhibitor
STI	Sexually Transmitted Infection
TFT	Thyroid Function Test
TVUSS	Transvaginal Ultrasound Scan
U&E	Urea and Electrolytes
USS	Ultrasound Scan

5. Referral Criteria for Menopause Clinic

Menopausal
- age 45 or over
- symptoms significantly affecting quality of life

Multiple treatment failure
- 3 or more regimens tried

Venous thromboembolism
- personal history, family history in a first-degree relative age <50 years old

Osteoporosis
- confirmed or high risk e.g. early menopause, corticosteroids > 5 mg prednisolone/day
- positive family history especially first-degree relative
- low bone density by DXA scan if available
- history of low trauma / fragility fracture

Previous or high risk of hormone dependent malignancy
- e.g. breast, ovarian or endometrial cancer. Details of disease including stage, treatment, family history
- Note: consider genetic counselling referral where is a family history of x1 first degree relative or x2 second degree relatives with breast, ovarian cancer and/or bowel.

Early menopause

Premature ovarian insufficiency

Other
- e.g. patient or GP directed

6. Information and Advice for Menopausal Women

Give information that includes:
- an explanation of the stages of the menopause
- common symptoms
- lifestyle changes and interventions that could help general health and wellbeing
- benefits and risks of treatments for menopausal symptoms
- long-term health implications of the menopause.

Explain that as well as a change in the menstrual cycle women may experience a variety of symptoms associated with menopause, including:
- vasomotor symptoms (e.g. hot flushes and sweats)
- musculoskeletal symptoms (e.g. joint and muscle pain)
- effects on mood (e.g. low mood)
- urogenital symptoms (e.g. vaginal dryness)
- sexual difficulties (e.g. low sexual desire).

Give information about the following types of treatment for menopausal symptoms:
- hormone replacement therapy (HRT)
- non-hormonal treatment, e.g. venlafaxine or gabapentin
- non-pharmaceutical options, e.g. cognitive behavioural therapy (CBT).

Give information about contraception to women who are in the perimenopausal phase - see Faculty of Sexual & Reproductive Healthcare guidance – ‘Contraception for Women Aged over 40 Years’ (3).

Offer women who are likely to go through the menopause as a result of medical or surgical treatment (including women with cancer, at high risk of hormone sensitive cancer or having gynaecological surgery) support and information about menopause and fertility before they have their treatment (1).

7. Diagnosis of Perimenopause and Menopause

Diagnose the following without laboratory tests in otherwise healthy women aged over 45 years with menopausal symptoms:

- perimenopause based on vasomotor symptoms and irregular periods
- menopause in women who have not had a period for at least 12 months and are not using hormonal contraception
- menopause based on symptoms in women without a uterus.

Take into account that it can be difficult to diagnose menopause in women who are on hormone treatment, e.g. Mirena for the treatment of heavy periods.

Do not use a serum follicle-stimulating hormone (FSH) test to diagnose menopause in women using combined oestrogen-progestogen contraception or high-dose progestogen.

Consider using a FSH test to diagnose menopause only:

- in women aged 40 to 45 years with menopausal symptoms, including a change in their menstrual cycle.
- in women aged under 40 years in whom menopause is suspected. In these women 2 x FSH measurements 6 weeks apart are needed for diagnosis.

8. Benefits and Risks of HRT

The main benefits of systemic HRT include:

- Reduction of vasomotor symptoms
- Improvement of low mood associated with the menopause
- Prevention and treatment of vulvo-vaginal (urogenital) atrophy
- Reduction of osteoporosis risk and fragility fractures
- Improvement of sexual function.

The risks of systemic HRT include:

- **Breast cancer -** current evidence suggests that oestrogen-only HRT is associated with little or no change in the risk of breast cancer while combined HRT can be associated with an increased risk which appears duration dependent and may vary with the type of progestogen used. However, this risk is low in both medical and statistical terms, particularly compared to other modifiable risk factors such as obesity and alcohol intake, and this should be taken in the context of the overall benefits obtained from using HRT (2). Local vaginal oestrogen is not associated with an increased risk in breast cancer (2). See Appendix 1 and 2 (4).

- **Venous thromboembolism -** the risk of venous thromboembolism (VTE) is increased by oral HRT compared with baseline population risk. However, the risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk. Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, e.g. BMI over 30 kg/m2. Consider referring menopausal women at high risk of VTE (for example, those with a strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

- **Cardiovascular disease -** Cochrane analysis suggests that HRT started before the age of 60, or within 10 years of the menopause, is associated with a reduction in atherosclerosis progression, coronary heart disease and death from cardiovascular causes as well as all-cause mortality.

- **Stroke -** oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke.

- **Dementia -** HRT is unlikely to increase the risk of dementia or to have a detrimental effect on cognitive function in women initiating HRT before the age of 60.

- **Ovarian cancer -** there may be a slight increase in the risk of developing serous and endometrioid ovarian cancer associated with HRT use.

- **Endometrial cancer -** unopposed oestrogen increases the risk of endometrial cancer. Use of sequential HRT for more than 5 years may be associated with an increase in risk. Continuous combined preparations are associated with significantly lower risk. Evidence suggests no increase in risk of recurrence with HRT in women with early stage endometrial cancer.

9. Pre-Existing Conditions and HRT

Contraindications to systemic HRT

HRT should not be prescribed to women in the following categories. Those with:

- pregnancy
- untreated hypertension
- active liver disease with abnormal liver function tests
- acute phase myocardial infarction
- acute phase arterial thromboembolic disease
- current venous thromboembolism
- undiagnosed vaginal bleeding or untreated endometrial hyperplasia
- known or suspected oestrogen-sensitive cancer, e.g. breast cancer
- porphyria cutanea tarda
- Dubin-Johnson and Rotor syndromes.

There are some conditions in which systemic HRT can only given with caution and after considering seeking specialist advice:

- **MI, CVA, Stoke, VTE - t**ransdermal oestradiol does not significantly increase event risk. Transdermal oestradiol is recommended in women with a pre-existing risk history. Oral oestradiol increases cardiac event risk and not recommended.
- **Family history of VTE** - if HRT is used transdermal route is preferred; consider specialist advice from haematologist.
- **Diabetes -** transdermal preparation preferred.
- **Endometriosis -** small risk of reactivation of endometriosis with HRT use. If HRT started after hysterectomy for endometriosis choice of HRT used should be influenced by extent of residual endometriosis and continuous combined HRT (at least for the first year post-op) might be indicated.
- **Epilepsy -** liver-enzyme inducing anti-epileptic drugs can increase the breakdown of HRT; low or standard dose oral HRT may be therefore ineffective and transdermal route is preferred.
- **Fibroids -** size of fibroids maybe increased with the use of HRT.
- **Gall bladder disease** - increased risk with HRT; transdermal preparations preferred.
- **Hyperlipidaemia -** triglycerides can increase with oral oestrogen: transdermal preparations preferred.
- **Hypertension** - should be controlled prior to starting HRT.
- **Migraine -** transdermal oestradiol is always recommended in women with a pre-existing risk history. Oral oestradiol is contraindicated in history of migraine with aura. Patches deliver a steady level of hormone which can also be helpful in conditions triggered by fluctuating hormone levels such as migraine.
- **Thyroid disease -** patients on thyroxine should have their thyroid function rechecked 3 months after starting HRT to see if the dose needs adjusting as HRT affects thyroid-binding globulin; transdermal HRT preferred.
- **Osteoporosis -** the 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 (1).
- **Breast cancer** - NICE menopause and locally and advanced breast cancer guidance do not recommend systemic HRT after a diagnosis of breast cancer. Lifestyle changes and non-hormonal alternatives are first-line management, apart from in exceptional circumstances when all other interventions have been tried and not helped. In such a situation it is recommended to that fully informed consent is documented, explaining the uncertainty about impact on risk of recurrence. It is also strongly recommended to liaise with the patient's oncologist. Topical vaginal oestrogen may be prescribed if vulvo-vaginal atrophy symptoms have proven refractory to vaginal moisturisers and lubricants but are contraindicated if a patient is taking an aromatase inhibitor (4).

10. Starting HRT

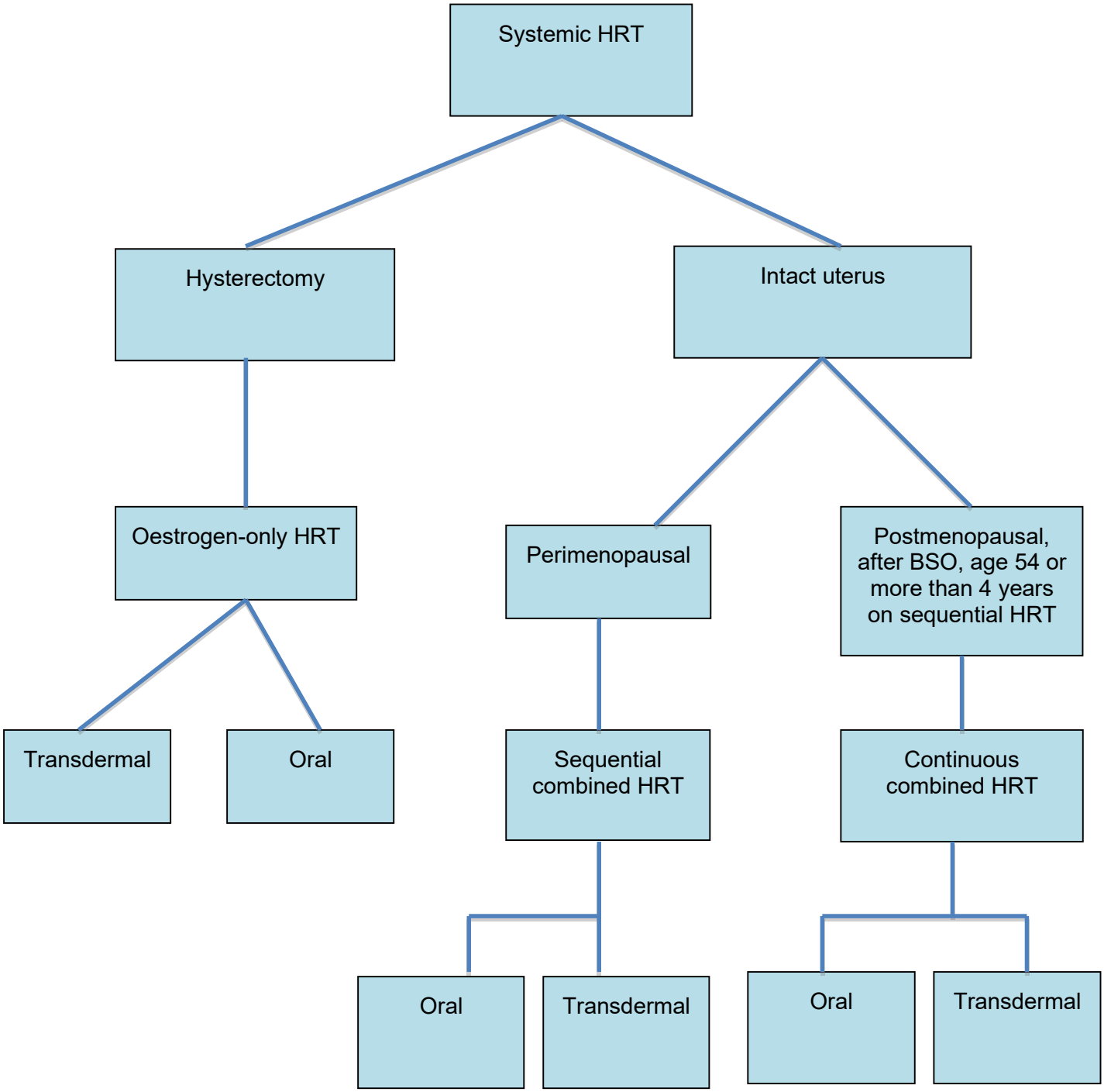
The decision whether to take HRT, the dose of HRT used and the duration of its use should be made on an individualised basis after discussing the benefits and risks with each patient. The choice of HRT for an individual depends on an overall balance of indication, risk-benefit profile, side effects and convenience. Aim to prescribe the lowest effective dose of HRT. Arbitrary limits should not be placed on the duration of usage of HRT.

The basic ground rules for prescribing HRT are set out in the flow chart below. Women with an intact uterus require oestrogen and progesterone / progestogen HRT. The progesterone (administered for 12–14 days in a sequential regimen and daily in a continuous combined regimen) is required to minimise the risk of endometrial hyperplasia and endometrial cancer associated with unopposed oestrogen exposure. Women who have had total hysterectomy (removal of uterus and cervix) can have oestrogen-only HRT.

Women who start sequential HRT before their periods stop may consider changing to a continuous combined therapy when they are 54 years of age or after four years of taking sequential HRT.

Continuous combined HRT can be given to postmenopausal women (LMP ≥ 1 year ago), after bilateral oophorectomy, women aged ≥ 54 years or after ≥ 4 years on sequential HRT. Giving continuous combined HRT to a woman with breakthrough ovarian activity is not dangerous but can be bothersome as irregular vaginal bleeding is likely.

Flowchart for prescription of systemic HRT



Choosing the best HRT regimen to start

HRT is licensed for symptom relief and osteoporosis prevention and treatment. Long term use should be individualised based upon informed consultation and risks versus benefits assessment. Choice of combination, type and route of HRT is dependent upon the woman's past medical history, menopausal status and uterine status. Hormone replacement should be individualised using the lowest effective dose to treat symptoms.

Oral HRT:

- generally cheaper and a common first line choice in primary care
- increases the production of clotting factors due to first pass effect
- associated with an increased risk of VTE
- increases SHBG and reduces free androgen index - this can result in loss of libido and increase tiredness
- increases triglycerides – caution when cardiac risk factors evident
- with combined oestrogen-progestogen tablet HRT there is less flexibility if you want to alter the dose of oestradiol and they all contain older synthetic progestogens
- there is less reliable absorption
- there are more contraindications to oral oestrogen (e.g. risk factors for VTE, migraine, etc).

Transdermal HRT:

- generally more expensive and usually first line choice in secondary care
- preferred route with history of CVD risk factors
- avoids first past metabolic effects
- neutral impact on SHBG
- neutral impact on lipids, lowers triglycerides
- lower incidence of adverse cardiovascular/VTE/stroke effects
- not associated with increased incidence of hypertension
- transdermal oestradiol may be administered by patch, gel (e.g. Oestrogel 0.06% gel or Sandrena gel) or spray (e.g. Lenzetto) - down to patient preference
- many women referred to secondary care have significant comorbidities or have struggled to find an HRT that suits them. For many of these women the best way forward is often transdermal oestrogen with oral micronised progesterone.
- with transdermal HRT it is easier to titrate the dose of oestradiol to control the patient's symptoms. This is straightforward for women who are on oestrogen only HRT.
- for women requiring titration of combined HRT it is best to administer the oestradiol transdermally and provide the progesterone component of the HRT as oral micronised progesterone (e.g. Utrogestan).

See Derbyshire Joint Area Prescribing Committee Formulary in appendix 4 for the different HRT brands available for prescription locally (5).

Choice of progesterone in combined HRT

The commonly used types of progestogens in combined HRT medications include norethisterone (e.g. in Elleste Duet or Kliofem tablets or Evorel Conti patches) or medroxyprogesterone (e.g. in Indivina tablets) or dydrogesterone (e.g. in Femoston tablets).

There is the option to administer the oestrogen and progesterone/progestogen as separate components, e.g. transdermal oestradiol and progesterone by mouth or via Mirena IUS.

Micronised progesterone (Utrogestan)

Many women seen in secondary care have comorbidities or other risk factors and for those who require combined HRT the current evidence suggests the optimal combination is transdermal oestradiol and oral micronised progesterone (Utrogestan). Micronised progesterone and dydrogesterone seem to be associated with lower risk of breast cancer and venous thrombosis compared to other progestogens. Micronised progesterone is available as Utrogestan 100 mg capsules and is used as per the following criteria on our local formulary:

- progesterone component of combined HRT.
- second line option for women requiring combined HRT but unsuitable for or intolerant of standard combination preparations. This patient group includes women at high risk of VTE (e.g. migraine, BMI >30, history of VTE) in whom transdermal oestrogen is recommended, but in whom Evorel Conti is not tolerated or unsuitable because of the need for variable oestrogen dose.
- The licensed dose is 200 mg at night for 12 days (Day 15 -26 of cycle) or 100 mg at bedtime from Day 1 -25 of cycle. Alternatively, women may be advised to take Utrogestan 200 mg at night for the first 14 days of each calendar month (cyclical) or 100 mg at night on a continuous

basis. This dosing regimen differs slightly from licensed dosing, however, is endorsed by BMS and more practical for women.

Mirena IUS

Mirena is a levonorgestrel-releasing intrauterine system (IUS) for use in combination with oestrogen as the progestogen component of HRT. Although it is licensed for 4 years for this indication, it's use for 5 years is endorsed by the Faculty of Sexual and Reproductive Healthcare and the British Menopause Society. The Mirena is particularly useful for women who experience vaginal bleeding on HRT, those requiring contraception, or those who suffer unacceptable side effects from the progestogen element of HRT.

11. Unscheduled Bleeding on HRT

Persistent unscheduled bleeding beyond 4–6 months from starting HRT warrants investigation with pelvic ultrasound scan assessment of the endometrial cavity and endometrial biopsy where appropriate or hysteroscopy and endometrial biopsy.

For the majority of women with unscheduled bleeding on HRT, modifying the progestogen intake will often control the bleeding especially in women who experience unscheduled bleeding in the first few months after starting HRT.

Progestogen intake can be modified as follows:

- For continuous combined HRT regimens, the dose of progestogen could be increased (e.g. increase micronised progesterone daily dose from 100 mg to 200 mg daily on continuous basis), particularly when combined with higher dose oestrogenic regimens. Those on continuous combined HRT regimens that contain a progestogen in a combined preparation or have the Mirena IUS, could have micronised progesterone, medroxyprogesterone acetate or norethisterone added to their HRT regimen. If they continue to experience ongoing unscheduled bleeding, the HRT regimen could be changed to a cyclical intake of progestogen.
- For cyclical HRT regimens, the dose of progestogen could be increased (e.g. micronised progesterone 300 mg for 14 days each month instead of 200 mg) or increase duration of progestogen intake (e.g. take progestogen for 21 days out of a 28-day HRT intake cycle).

Women who continue to have unscheduled bleeding beyond six months despite modifying their progestogen intake, or where there is a concern about the clinical presentation or bleeding amount / pattern, should have pelvic ultrasound scan assessment of the endometrial cavity and an endometrial biopsy where appropriate or hysteroscopy and endometrial biopsy.

If breakthrough bleeding occurs following the switch to continuous combined HRT and does not settle after three to six months, then the woman can be switched back to a sequential regimen for another year.

The risk of endometrial cancer in women with unscheduled bleeding on HRT is significantly lower than that with postmenopausal bleeding in women not on HRT especially in women who had not been experiencing bleeding before commencing HRT and who are taking progestogen.

12. Review After Starting HRT

Review each treatment for short-term menopausal symptoms:

- at 3 months to assess efficacy and tolerability
- annually thereafter unless there are clinical indications for an earlier review (such as treatment ineffectiveness, side effects or adverse events).

13. Stopping HRT

Arbitrary limits should not be placed on the duration of usage of HRT.

Offer women who are stopping HRT a choice of gradually reducing or immediately stopping treatment. Gradually reducing HRT may limit recurrence of symptoms in the short term but gradually reducing or immediately stopping HRT makes no difference to their symptoms in the longer term.

14. Alternatives to HRT

Non-hormonal interventions may be of help in women who have a contraindication to HRT or who do not wish to take HRT.

Lifestyle modifications to help with hot flushes and night sweats include regular exercise, weight loss, lighter fitting clothing, keeping the environment at a lower temperature, reducing stress and avoiding triggers such as caffeine, smoking, alcohol and spicy foods. Sleep problems might be helped by avoiding exercise late in the day and having a regular bedtime. Mood can be elevated by physical activity, relaxation techniques and ensuring adequate sleep.

Some women may ask about complimentary therapies, but it should be advised that there is a lack of evidence around their use. The quality, purity and constituents of complementary therapies may be unknown. There is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms but multiple preparations are available and their safety is uncertain and interactions with other medicines have been reported. St John's wort may be of benefit in the relief of vasomotor symptoms in women with a history of, or at high risk of, breast cancer, although there is uncertainty about the appropriate dose, persistence of effect, variation in the nature and potency of preparations and potential serious interactions with other drugs (including tamoxifen, anticoagulants and anticonvulsants).

If HRT is contraindicated or the woman does not wish to take it, there are other non-hormonal options that can be given. For vasomotor symptoms, venlafaxine 37.5 mg oral twice daily or paroxetine 10 mg oral daily can be tried. However, it should be noted that these are off-label use and so efforts should be made to consider withdrawal of treatment if women have been symptom-free for 1-2 years. Women experiencing fluctuating mood may be referred to self-help groups, for cognitive-behavioural therapy or offered antidepressants. However, it should be explained that there is no actual evidence for using antidepressants to improve mood in menopausal women who do not have a diagnosis of depression.

15. Urogenital Atrophy (5)

Vulval, vaginal and urinary symptoms caused by oestrogen deficiency are very common in menopausal women and easily treatable. Patients need to be examined as other vulval conditions such as lichen sclerosus or vulval intra-epithelial neoplasia (VIN) could be otherwise missed.

The principles of management are to restore urogenital physiology and to alleviate symptoms. The correct treatment can relieve symptoms and considerably transform a woman’s quality of life.

As a lack of circulating, natural oestrogen is the primary cause of atrophic vaginitis, hormone replacement therapy and/or localised hormone treatment are the most logical choice of treatment and have been shown to be effective in the restoration of anatomy and the resolution of symptoms.

Systemic hormone replacement therapy
Systemic HRT can be very effective when given to women with other symptoms of the menopause (or perimenopause) in addition to symptoms of urogenital atrophy.

Around 10–25% of women who take systemic HRT will have urogenital symptoms that persist. These women can be given vaginal local oestrogen in addition to taking HRT. It is important that all women taking HRT are asked about any genital symptoms in their annual review.

Vaginal oestrogen
Oestrogen replacement restores normal pH levels and thickens and revascularises the vaginal epithelium. There is also a decreased incidence of urinary tract infections and urinary symptoms.

Women should be given treatment initially for three months and then be offered a review. After this time, treatment can then be put on a repeat prescription by the GP. It is preferable to start treatment early, rather than waiting for symptoms to worsen. If treatment is started earlier on, it helps restore the anatomy back to normal and prevents more severe changes occurring, such as labial resorption or clitoral atrophy.

The clinical response to treatment with topical oestrogen is usually rapid and sustained.

Topical vaginal oestrogen has minimal risks and is safe for most of women for as long as required which might be many years. There are very few contraindications to topical oestrogen - the only relative contraindication is a past history of a hormone-dependent tumour, e.g. breast cancer.

If vaginal oestrogen does not relieve symptoms of urogenital atrophy, consider increasing the dose. Vaginal moisturisers and lubricants can be used alone or in addition to vaginal oestrogen.

Do not offer routine monitoring of endometrial thickness during treatment for urogenital atrophy. It is not necessary to use progesterone for endometrial protection when using standard doses of vaginal oestrogen long term.

Vaginal oestrogen can be absorbed from the vagina and surrounding area via a pessary, cream, gel or vaginal ring. There are two types of oestrogen used – oestradiol and oestriol.

The dose of vaginal oestrogen is very low; for example, using 10 mcg oestradiol pessaries regularly for one year is an equivalent dose to just one 1 mg oestradiol HRT tablet.

Vaginal oestrogen preparations:

- intravaginal creams:
    - Estriol 0.1% (Ovestin) - delivers same dose per applicator as estriol 0.01% in a smaller volume and is more cost effective
    - Estriol 0.01% - (Gynest® brand discontinued, now only available as generic).

- vaginal gel (Blissel) estriol 50 micrograms/g
- vaginal tablet (Vagifem) estradiol 10 mcg.
- vaginal Ring (Estring) estradiol 7.5mcg/24hr
- vaginal pessary (Imvaggis) estriol 30 mcg

16. Altered Sexual Function and the Menopause

Levels of testosterone gradually decline with increasing age or reduce abruptly following oophorectomy. The most commonly described symptoms of androgen insufficiency include reduced libido, dysphoric mood, fatigue, bone loss, and decreased muscle strength.

Reduced libido is common in menopausal women. NICE guidelines state that testosterone supplementation can be considered for menopausal women with low sexual desire if hormone replacement therapy alone is not effective.

Numerous studies have shown that adding testosterone to hormonal therapy can improve sexual function and general wellbeing among women during their menopause.

Practical points

- check the patient is well oestrogenised before starting (i.e. no vasomotor symptoms).
- calculate free androgen index (FAI). FAI = total testosterone / SHBG × 100. If in the lowest quartile (<1%) consider a trial of testosterone.
- Check FAI after starting treatment and aim to keep it <5%.

There are currently no available licensed preparations for women in the UK. The BMS has released guidance on prescription of testosterone which suggests some of the products that can be used and their doses (7).

Commonly used testosterone replacement in menopause

- Testogel 1% testosterone gel in 5 g sachets containing 50 mg testosterone: starting dose 1/10 of a sachet/day = 5 mg/day, that is, each sachet should last 10 days.
- Tostran 2% testosterone gel in a canister containing 60 g: starting dose 1 metered pump dispenses 0.5 g of gel, providing 10 mg of testosterone for application to the skin on alternate days - each canister should last 240 days.

It can sometimes take several weeks or even months for a woman to notice the beneficial effects of testosterone. If they have not noticed an improvement after 6 months, then it is unlikely to be beneficial.

Testosterone appears to be safe when used transdermally and in low doses. There are little long-term safety data on the use of testosterone in menopausal women beyond 2 years. What is available is reassuring in that transdermal testosterone is not associated with an increase in blood pressure and has no adverse effects on lipid profile.

Side effects can occasionally occur including acne and increased hair growth at the site of application, but increase in facial hair, alopecia, or voice deepening does not occur if testosterone levels are kept within the female physiological range.

17. Premature Ovarian Insufficiency

The European Society of Human Reproduction and Embryology has published comprehensive evidence-based guidelines on the management of POI [8]. Diagnosis and management is also included in the NICE NG23 Menopause guidance [2]. The pathogenesis of Premature Ovarian Insufficiency (POI) is poorly understood. Approximately 90-95% of women with spontaneous POI will have no underlying cause identified. The increased life expectancy now seen with juvenile and young adult cancers means that many women will be surviving decades following an iatrogenic menopause. The incidence of POI under 40 in the general population is 1-5%. Between 2-8% may have identifiable genetic or autoimmune causes although this may be widely under reported. The long term sequelae include premature cardiovascular disease, osteoporosis and cognitive impairment.

If POI is suspected, consider referring them to the Joint Gynaecology-Endocrinology Clinic, run jointly by a reproductive medicine specialist and endocrinologist at Royal Derby Hospital.

Diagnosing premature ovarian insufficiency

- take into account the woman's clinical history (for example, previous medical or surgical treatment) and family history when diagnosing premature ovarian insufficiency.
- diagnose premature ovarian insufficiency in women aged under 40 years based on:
    - menopausal symptoms, including no or infrequent periods (taking into account whether the woman has a uterus) and
    - elevated FSH levels on 2 blood samples taken 4–6 weeks apart.
- do not diagnose premature ovarian insufficiency on the basis of a single blood test.
- do not routinely use anti-Müllerian hormone testing to diagnose premature ovarian insufficiency.

Investigations

- karyotype and molecular genetics: chromosomal analysis and Fragile X pre-mutation testing
- autoimmune antibodies: adrenal, thyroid. Ovarian antibodies can be performed but it is more theoretical and its clinical use is limited.
- imaging: transvaginal ultrasound scan
- radiology: baseline DXA scan then every 3- 5 years.

Managing premature ovarian insufficiency

- Hormone replacement should be offered in the form of HRT or combined hormonal contraception (CHC) unless contraindicated (for example, in women with hormone-sensitive cancer)
- CHC is peer friendly, simple and provides contraception
- Explain to women with premature ovarian insufficiency:
    - the importance of starting hormonal treatment either with HRT or a combined hormonal contraceptive and continuing treatment until at least the age of natural menopause (unless contraindicated)
    - Compliance, patient choice, co-morbidities and contraceptive needs will dictate choice
    - that 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
    - that both HRT and combined oral contraceptives offer bone protection
    - HRT may have a beneficial effect on bone mineralisation and blood pressure compared to the CHC
    - higher oestrogen levels may be required to maintain wellbeing and protect bone density
    - risks associated with HRT are not presumed to apply in women with POI as physiologically normal levels are being maintained with like for like hormones

    - Spontaneous ovulation may continue or return, therefore contraceptive needs must be discussed and documented. Refer to fertility clinic for advice on fertility options including ovum donation
    - testosterone replacement may be indicated for low libido
- Give women with premature ovarian insufficiency and contraindications to hormonal treatments advice, including on bone and cardiovascular health, and symptom management.
- If adolescent girls or young women presenting with primary amenorrhoea and diagnosed to have POI along with absent secondary sexual characteristics, they will need initial oestrogen therapy to help with breast development and other secondary sexual characteristics. Specialist clinic referral (Joint Gynae-Endocrine clinic) is recommended.

Follow up and discharge

Once established on treatment, to ensure good compliance, reviews should occur annually:

- consider discharge from age 45, with normal bone density and ongoing care with the GP
- HRT is required until the average age of the menopause.

18. Monitoring Compliance and Effectiveness

As per the Business Unit audit forward programme

19. References

1. Menopause: diagnosis and management NICE guideline. Published: 12 November 2015. www.nice.org.uk/guidance/ng23.

2. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women.

3. Faculty of Sexual & Reproductive Healthcare guidance – 'Contraception for Women Aged over 40 Years'.

4. BMS Consensus Statement: The risks and benefits of HRT before and after a breast cancer diagnosis. BMS February 2020.

5. Derbyshire Joint Area Prescribing Committee Menopause Management Guideline, March 2020.

6. Newson l, Kirby M, Stillwell S, Hackett G, Ball S, Lewis R Position Statement for Management of Genitourinary Syndrome of the Menopause, BSSM 2021. http://www.bssm.org.uk › uploads › 2021/03 › G...

7 Panay N. Testosterone replacement in menopause. 2019. https://thebms.org.uk/publications/tools-for-clinicians/testosterone-replacement-in-menopause/ accessed 21 Feb 2020

8. European Society of Human Reproduction and Embryology – Management of Women with Premature Ovarian Insufficiency Dec 2015.

(BMS Consensus Statement: The risks and benefits of HRT before and after a breast cancer diagnosis. BMS February 2020).

Table 1 compares the absolute excess risk with current HRT use from the randomised WHI, 2019 CGHFBC and 2015 NG23. Overall, the absolute excess risk of diagnosis with HRT use is small, regardless of category of current use. Most women exposed to HRT will not be diagnosed with breast cancer as a result of exposure.

Absolute excess risk of breast cancer diagnosis over 10 years per 1000 women starting HRT at age 50

	Duration of HRT use	HR or RR (95% CI)	Absolute Excess Risk	Women diagnosed	Women not diagnosed
No HRT				26	974
Oestrogen alone		—	—		
Use up to 5 years					
WHI study 2013	4.6 yrs (median)	0.62 (0.32-1.18)	-10 (-18-+5)	16	984
NICE 2015	Up to 5 years	1.16 (0.95-1.42)	+4 (-1-+11)	30	970
CGHFBC 2019*	< 5 years	1.16 (1.10-1.24)	+4 (2-6)	30	970
Use up to 10 years					
WHI study 2013	No data	—	—	—	—
NICE 2015*	5-10 years	1.23 (0.94-1.61)	+6 (-2-+16)	32	968
CGHFBC 2019*	5-9 years	1.22 (1.17-1.28)	+6 (4-7)	32	968
Combined HRT					
Use up to 5 years					
WHI study 2013	3.2 yrs (median)	1.06 (0.67-1.67)	+2 (-12-+17)	28	972
NICE 2015	Up to 5 years	1.52 (1.25-1.85)	+14 (7-22)	40	960
CGHFBC 2019	< 5 years	1.56 (1.49-1.64)	+15 (13-17)	41	959
Use up to 10 years					
WHI study 2013	No data	—	—	—	—
NICE 2015**	5-10 years	1.94 (1.41-2.66)	+24 (11-43)	50	950
CGHFBC 2019	5-9 years	1.97 (1.90-2.04)	+25 (23-27)	51	949

* The risk estimate for less than 5 years category has been calculated by pooling the numbers for < 1year and 1 to 4 years duration of HRT exposure, using inverse variance weighting.

**Evidence on observational estimate demonstrated very serious imprecision in the estimate of effect.

(BMS Consensus Statement: The risks and benefits of HRT before and after a breast cancer diagnosis. BMS February 2020).

Table 2 shows comparative absolute risks in women with a previous duration of HRT use up to five years from the 2019 CGHFBC and randomised WHI study.

Absolute excess risk of breast cancer diagnosis over 10 years per 1000 women starting HRT at age 50 with previous HRT exposure, by duration of use and time since stopping

Prior duration of HRT use, 5 years	Time since last use	HR or RR (95% CI)	Absolute Excess Risk	Women diagnosed	Women not diagnosed
Past use of oestrogen					
No HRT		—	—	**26**	**974**
Time since stopping up to 5 years					
WHI study 2013, 2015	2.75 years*	0.55 (0.34-0.89)	-11 (-17-+3)	15	985
CGHFBC 2019	< 5 years††	1.05 (0.96-1.16)	+1 (-1-+4)	27	973
Time since stopping 5 to 9 years					
WHI study 2013, 2015	6.6 years**	1.17 (0.73-1.87)	+4 (-6-+23)	30	970
CGHFBC 2019	5-9 years	1.06 (0.97-1.16)	+2 (-1-+4)	28	972
Past use of combined HRT					
Time since stopping up to 5 years					
WHI study 2013, 2015	2.75 years*	1.23 (0.90-1.70)	+6 (3-18)	32	968
CGHFBC 2019	< 5 years††	1.13 (1.05-1.21)	+3 (1-5)	29	972
Time since stopping 5 to 9 years					
WHI study 2013, 2015	8.2 years†	1.37 (1.06-1.77)	+10 (2-20)	36	964
CGHFBC 2019	5-9 years	1.21 (1.14-1.29)	+5 (4-8)	31	969

* Duration of the early intervention phase post HRT cessation.
**,† Duration of late intervention phase in the oestrogen only and combined HRT arms.
†The risk estimate for less than 5 years category has been calculated by pooling the numbers for < 1year and 1 to 4 years duration of HRT exposure, using the inverse variance weighting.

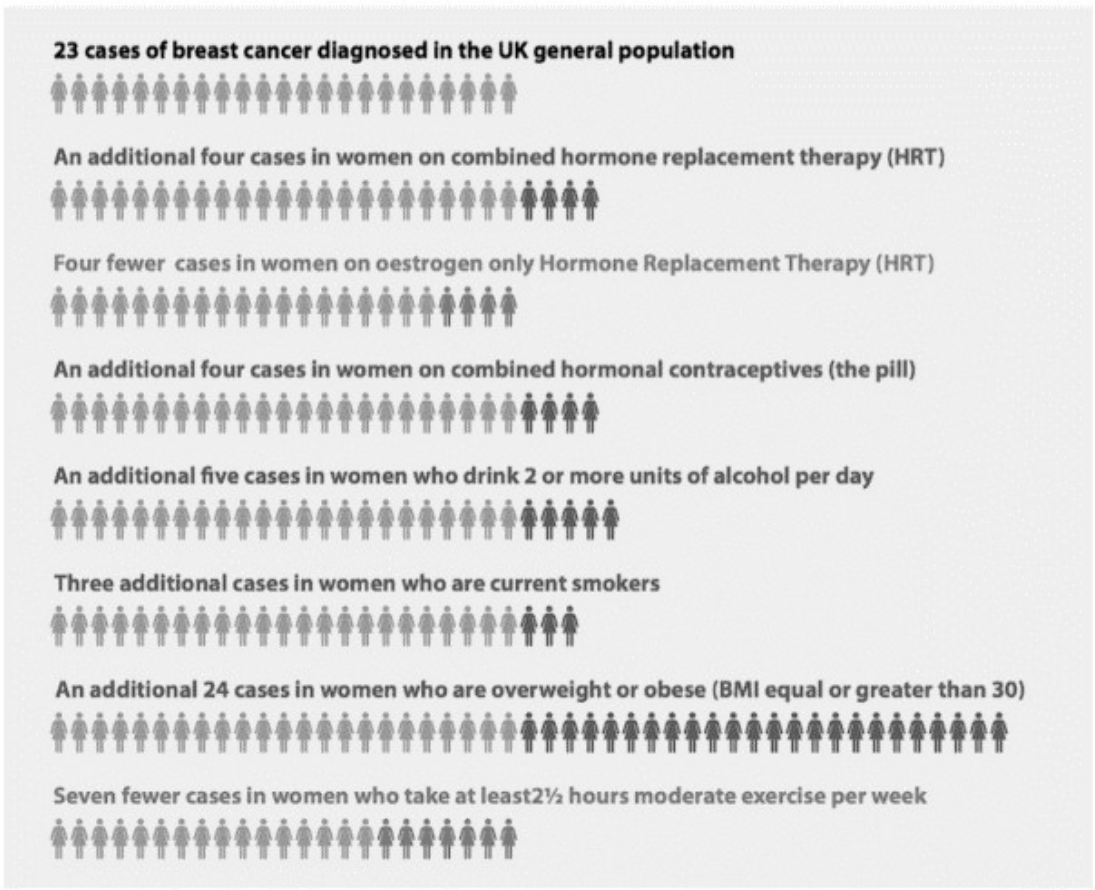
Understanding the risks of breast cancer

Women's Health Concern

A comparison of lifestyle risk factors versus Hormone Replacement Therapy (HRT) treatment.

Difference in breast cancer incidence per 1,000 women aged 50-59.
Approximate number of women developing breast cancer over the next five years.

NICE Guideline, Menopause: Diagnosis and management November 2015



Women's Health Concern

www.womens-health-concern.org
Reg Charity No: 279651
Company Reg No: 1432023

Women's Health Concern is the patient arm of the BMS.
We provide an independent service to advise, reassure and educate women of all ages about their health, wellbeing and lifestyle concerns.

Go to **www.womens-health-concern.org**

BMS British Menopause Society

www.thebms.org.uk
Reg Charity No: 1015144
Company Reg No: 02759439

March 2017

Appendix D

Hormonal content of formulary HRT preparations (Prices as per MIMs January 2020)

Below are preferred formulary choices. Alternatives may be preferred on an individual basis.

OESTROGEN ONLY	Formulation	Oestrogen	Strength	Progestogen	3months cost
Elleste Solo	1st line tablet	Estradiol	1mg 2mg	--	£5.06
Zumenon	Tablet- alternative If unable to obtain Ellest Solo	Estradiol	1mg 2mg	--	£6.90
Premarin*	2nd line tablet	Conjugated equine oestrogens	300mcg 625mcg 1.25mg	--	£6.07 £4.02 £3.58
Evorel	24h patch (replace every 3-4 days)	Estradiol	25mcg,50mcg 75mcg,100mcg	--	£10.26 £11.66 £12.36 £12.84
Estraderm MX	24h patch- alternative if unable to obtain Evorel	Estradiol	25, 50 mcg 75 mcg 100 mcg	--	£16.5 £19.26 £19.98
Oestrogel	Transdermal gel	Estradiol	0.06%	--	£12.6 - £25.2
Sandrena	Transdermal gel	Estradiol	500mcg, 1mg	--	£15-£17.57
Lenzetto	Transdermal spray	Estradiol	1.53mg per actuation	--	£11.08 - £22.17
SEQUENTIAL COMBINED	**Formulation**	**Oestrogen**	**Strength**	**Progestogen**	**Cost for 3 months**
Elleste Duet	1st line tablet	Estradiol	1mg, 2mg	Norethisterone 1mg	£9.20
Novofem	Tablet- alternative sequential combined HRT	Estradiol	1mg	Norethisterone 1mg	£11.43
Femoston	2nd line tablet	Estradiol	1mg, 2mg	Dydrogesterone 10mg	£16.16
Evorel sequi	Patch (replace every 3-4 days)	Estradiol	50mcg	Norethisterone 170mcg	£33.27
CONTINUOUS COMBINED	**Formulation**	**Oestrogen**	**Strength**	**Progestogen**	**Cost for 3 months**
Premique low dose*	1st line tablet	Conjugated oestrogens	300mcg	Medroxyprogesterone 1.5mg	£6.52
Kliofem	1st line tablet	Estradiol	2mg	Norethisterone 1mg	£11.43
Kliovance	Tablet- alternative continuous combined HRT	Estradiol	1mg	Norethisterone 500mcg	£13.20
Indivina	2nd line tablet	Estradiol	1mg, 1mg, or 2mg	Medroxyprogesterone 2.5mg, 5mg or 5mg	£20.58
Femoston conti	2nd line tablet	Estradiol	0.5mg, 1mg	Dydrogesterone 2.5mg, 5mg	£24.43
Evorel Conti	Patches	Estradiol	50mcg/24hr	Norethisterone 170mcg	£37.22

*the oestrogen in Premarin and Premique is horse oestrogen (from pregnant horse urine), these may not be acceptable to all women; all other preparations in which the oestrogens are identical to human oestrogens

Appendix E

Equivalent doses of oestradiol:

Low dose – oral oestradiol 0.5 mg / 1 mg, conjugated oestrogens 300 mcg, oestradiol patch 25 / 37.5 mcg

Standard dose - oestradiol 2 mg, conjugated oestrogens 625 mcg, oestradiol patch 50 mcg, Oestrogel 2 measures

High dose - oestradiol patch 75 / 100 mcg, Oestrogel 4 measures, conjugated oestrogens 1.25 mg

Documentation Control

Reference Number: UHDB/Gynae/11:22/M2	**Version: 1**		**Status: FINAL**	
Version Amendment	**Version**	**Date**	**Author**	**Reason**
	1	August 2022	Mr J R Allsop – Consultant Obstetrician & Gynaecologist	New
Intended Recipients: Clinical staff undertaking this procedure				
Training and Dissemination: Cascaded through lead doctors, senior nurses, published on Intranet (KOHA) & Email: NHS.net circulation list				
Consultation with:	Gynaecology Staff			
Business Unit sign off:	10/10/2022: Gynaecology Guidelines Group: Miss B Purwar – Chair 18/10/2022: Gynaecology Development & Governance Committee: Mr J Dasgupta (Virtual sign off)			
Divisional sign off:	25/10/2022			
Implementation date:	21/11/2022			
Review date:	October 2025			
Key Contact:	Cindy Meijer			