Based on NHS Stockport CCG HRT Guidance for Menopause Management

Hormone Replacement Therapy Guidance for Menopause Management

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Version 1.0

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The latest and master versions of this document are held by the GMJCT Strategic Medicines Optimisation

Copies of this document can be obtained at gmmmg@nhs.net from the Strategic Medicines Optimisation Team, Greater Manchester Joint Commissioning Team (GMJCT)

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Approvals

This document must be approved by the following before distribution:

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Final version available on GMMMG website

Contents

Abbreviations used in the guidance	
BMS	British Menopause Society
CCHRT	continuous combined HRT
CEE	conjugated equine oestrogen
COCP	combined oral contraceptive pill
E2	17β estradiol
FAI	free androgen index
FSH	follicle-stimulating hormone
FSRH	the Faculty of Sexual and Reproductive Healthcare
GSM	genitourinary syndrome of menopause
IMP	implant
IUS	intrauterine system
LMP	last menstrual period
LNG-IUS	levonorgestrel-releasing intrauterine system
MPA	medroxyprogesterone acetate
POI	premature ovarian insufficiency
POP	progesterone only pill
Seq HRT	sequential combined HRT
SHBG	sex hormone binding globulin

Glossary of terms used in the guidance	
Continuous combined HRT	Oestrogen and progestogen are taken daily
Early menopause	This term is used for the women who go through menopause between 40-45 years
Genitourinary syndrome of menopause (GSM)	Genitourinary syndrome of menopause (GSM), also known as vaginal atrophy, urogenital atrophy, and vulvovaginal atrophy, affects nearly 50% of menopausal women. It is due to hormonal deficiency affecting the urogenital area, including vagina, vulva, and urinary tract
Hypoactive sexual desire disorder	A continued lack of interest in sexual activities and sexual fantasies (which is causing stress in the relationship) diagnosed after excluding all the other factors such as relationship issues, vaginal changes at menopause, low mood and other things that can indirectly affect sexual desire
Perimenopause	The perimenopause is also known as the menopausal transition or climacteric and it usually occurs between ages of 45 and 50. During this time a woman has irregular cycles, which are anovulatory and experiences menopausal symptoms
Menopause and postmenopause	This is when a woman has permanent cessation of periods for 12 consecutive months and is a retrospective diagnosis. The average age of menopause is 51 in the UK. Symptoms can occur between ages of 45 and 55. Post menopause is one year since periods have stopped and thereafter.
Premature ovarian insufficiency	Menopause occurring before the age of 40 years (also known as premature ovarian failure or premature menopause). It can occur naturally (including auto-immune, genetic causes) or as a result of medical (including chemotherapy and radiotherapy) or surgical treatment.
Sequential/cyclical combined HRT	**Monthly cyclical regimen** - oestrogen is taken daily and progestogen is given for 10–14 days every month, depending on the type of progestogen. **Three-monthly cyclical regimen** - oestrogen is taken daily and progestogen is given for 14 days every 13 weeks
Subtotal hysterectomy	Hysterectomy can either be total, where both the uterus and cervix are removed, or sub-total, where uterus is removed but the cervix is retained.
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 vulval and vaginal dryness, irritation, discomfort, soreness recurrent infections and urinary symptoms of frequency, urgency, 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. This is caused by decrease in oestrogen which results in decrease in serotonin, increase in sympathetic activity and increase signalling of neurotransmitters such as neurokinin B in the thermoregulatory centre, situated in the hypothalamus.

	These symptoms can have a major impact on activities of daily living.

1. Introduction[1,2]

This document aims to provide advice and guidance on diagnosing the menopause and prescribing hormone replacement therapy (HRT) for women as recommended in NICE guideline (NG23) Menopause: diagnosis and management.

The guidance recognises that HRT is an effective treatment for menopausal symptoms, particularly for the management of vasomotor symptoms (including night sweats and hot flushes), musculoskeletal symptoms, psychological symptoms (including low mood), urogenital atrophy, altered sexual function and sleep disturbances.

Whilst this guideline focuses on HRT treatment, lifestyle modifications can also improve vasomotor symptoms and improve quality of life and long-term health. Lifestyle modifications which should be discussed with patients include taking regular exercise, maintaining, or achieving a normal body mass index, reducing alcohol intake, and stopping smoking. Sleep disturbance may be helped by sleep hygiene measures and mood disturbance can be improved with relaxation, exercise, and CBT.

Please refer to the Menopause Practice Standards for further information.

2. Diagnosis of menopause, perimenopause, early menopause, and premature ovarian insufficiency. Indications for FSH testing [1,2]

2.1 Women over 45

- Diagnosis of menopause and perimenopause is based on clinical symptoms experienced by a woman
- Diagnose menopause in women with uterus who has not had a period for at least 12 months (and is not using hormonal contraception) and in women without uterus based on symptoms
- Do not routinely perform follicle-stimulating hormone (FSH) test to diagnose menopause and perimenopause in women over 45 years of age, unless there is uncertainty about the diagnosis or suspicion of other pathology. Be advised that FSH testing is not appropriate in women who are already taking HRT or combined hormonal contraception
- The average age of menopause is 51, however women can experience symptoms between 45 and 55, during perimenopause and menopause

2.2 Women age 40-45

- Diagnosis of an early menopause should be based on the presence of menopausal symptoms and oligomenorrhoea/amenorrhoea of more than 3 months duration with elevated FSH (FSH> 30 IU/L) on at least 2 occasions measured 4-6 weeks apart.
- FSH testing is not suitable in woman taking combined hormonal contraception (or HRT)
- If diagnosis is inconclusive seek advice from a menopause specialist

2.3 Women under age of 40

- Diagnosis of premature ovarian insufficiency (POI), provided a woman is not taking combined hormonal contraception, should be based on the presence of menopausal

symptoms and oligomenorrhoea/amenorrhoea of more than 3 months duration with elevated FSH (FSH> 30 IU/L) on at least 2 occasions measured 4-6 weeks apart

- If diagnosis of POI is inconclusive rule out other causes of the presented symptoms and absent periods and consider referral, or seek advice from a menopause specialist
- For further information on diagnosing and managing POI see NICE CKS on Diagnosing of POI and refer to section 3.2 of this guideline.

3. Indications for HRT [1,2,3,4,5,6,7,8,9,10,11]

3.1 Menopause and perimenopause

HRT is beneficial for a wide range of menopausal symptoms and consequently is improving woman's quality of life. All women should be provided with adequate information on the treatment choice which should be then individually tailored to the woman's needs. Short- and long-term benefits versus risks should be assessed in each case.

Commonly experienced menopausal symptoms include the following: vasomotor symptoms, cognitive symptoms and mood disorders, sleep disturbances, fatigue, tiredness and low energy levels, loss of sexual desire and libido, joint and muscle pains, headaches, and genitourinary symptoms.

3.1.1 Vasomotor symptoms

- Offer women HRT as first line treatment for vasomotor symptoms.
- As per NICE, non-HRT options include clonidine or selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), however these should only be offered to women who are unable or do not wish to take HRT alone

3.1.2 Psychological symptoms

- Consider HRT to alleviate low mood that arises as a result of the menopause.
- Consider cognitive behavioural therapy (CBT) to alleviate low mood or anxiety that arise as a result of the menopause.
- There is no clear evidence for SSRIs or SNRIs to ease low mood in menopausal women who have not been diagnosed with depression (see the NICE guideline on depression in adults).

3.1.3 Altered sexual function

- Consider testosterone supplementation (unlicensed) for menopausal women with low sexual desire if HRT alone is not effective, and other causes of low sex drive have been ruled out

3.1.4 Urogenital atrophy (genitourinary syndrome of menopause)

- Offer vaginal oestrogen to women with urogenital atrophy (including those on systemic HRT) and continue treatment for as long as needed to relieve symptoms and review the need for continuing treatment at least annually

3.2 Premature ovarian insufficiency (POI)

- Women with POI should take HRT (or a combined hormonal contraception) up to the average age of the natural menopause (51 years in the UK), after which the need for ongoing treatment should be reassessed and HRT can be continued beyond 51 years of age if benefits outweigh risks
- HRT and combined oral contraceptive pill (COCP) are suitable options to consider in POI. While HRT may result in a more favourable improvement in bone density and cardiovascular markers compared to the COCP, it is not a contraceptive Women who opt to choose HRT will require additional contraception as spontaneous ovulation and pregnancies have been reported in 5-10 % of cases.

3.3 Subtotal hysterectomy

- If the uterus has been removed but the cervix left in place, it is uncertain whether HRT can be given in the form of oestrogen-only or whether oestrogen combined with progestogen is necessary.
- Endometrium may still be present in the cervical canal, and this could become thickened from oestrogen stimulation
- Progestogen challenge is advised for 3 months with oestrogen combined with sequential progestogen e.g., sequential combined HRT
- If there is monthly bleeding with oestrogen combined with sequential progestogen it means that endometrial cells are present and are responding to the hormones; therefore, both oestrogen and progestogen should be used thereafter. If a woman would like to avoid monthly bleeding, continuous combined HRT is advised.
- If there is no bleeding present with first 3 months of oestrogen combined with sequential progestogen, then oestrogen can be given on its own.

3.4 Endometrial ablation

- British Menopause Society (BMS) advises that combined HRT regimens (sequential or continuous combined) should be used in women who have undergone endometrial ablation and who wish to take HRT
- If after endometrial ablation there are still light periods, sequential HRT should be offered for the first 1-2 years
- If after endometrial ablation there are no periods, continuous combined HRT is recommended (patients may experience irregular bleeding as a side effect of the HRT for the first 6 months)
- There is potential risk of complications if IUS Mirena® is used after endometrial ablation therefore IUS Mirena® is not recommended

3.5 Severe endometriosis with or without hysterectomy

- In hysterectomised women continuous combined HRT or tibolone could be started for at least the first few years after surgery. This may be then changed to oestrogen only HRT due to a possible better safety profile in women over the age of natural menopause, however this needs to be balanced with the theoretical risk of reactivation and malignant transformation of any residual endometriosis
- Hysterectomised women with endometriosis and refractory symptoms should be referred to the specialist in menopause

- Women with uterus and severe endometriosis who experience menopause like symptoms can be offered continuous combined HRT, tibolone or oestrogen with Mirena®
- For further information about endometriosis and induced menopause see BMS: Induced menopause in women with endometriosis

3.6 Prevention and treatment of osteoporosis in patients under the age of 60 with menopausal symptoms

- Menopause is one of the risk factors for osteoporosis
- Women with untreated early menopause and POI are at risk of osteoporosis and HRT is the treatment of choice for osteoporosis prevention and relief of menopausal symptoms
- HRT therapy might be considered for the treatment of postmenopausal osteoporosis in women under age of 60, who also experience menopausal symptoms, after assessing risk and benefits of the treatment.
- When selecting drug treatment option for osteoporosis consider the severity of fracture risk, any additional risk factors, and patient choice.
- Treatment options for patients with moderate to high risks of fracture need to be discussed with rheumatologist to decide if other osteoporosis treatments are necessary

4. Contraindications for prescribing of HRT[1,2,3]

- Pregnancy
- Active unexplained vaginal bleeding
- Previous idiopathic or current venous thromboembolism (VTE) (deep vein thrombosis or pulmonary embolism), unless the woman is already on anticoagulant treatment
- Active or recent arterial thromboembolic disease (e.g., MI or angina)
- Active liver disease with abnormal liver function tests (LFTs)
- Breast cancer (suspected, current or past). Women who do not respond to the non-hormonal treatment should be referred to menopause specialist and oncology team to discuss suitable treatment options
- Known or suspected oestrogen dependent cancers (including endometrial cancer)
- Thrombophilic disorders
- Untreated endometrial hyperplasia

5. Cautions for prescribing HRT[1,2,12,13,14,15,16, 17]

5.1 Perimenopausal depression

- The appropriate choice of HRT progestogen is paramount in treating perimenopausal depression
- Women with a history of premenstrual syndrome and postnatal depression have a higher risk of depression during their menopause.
- Women with perimenopausal depression are often intolerant to more androgenic progestogens (such as norethisterone and medroxyprogesterone) which are best to be avoided in these women
- Micronised progesterone and dydrogesterone (only available as combined HRT) are associated with fewer side-effects than the more androgenic progestogens and could be considered in women with perimenopausal depression

5.2 Women over 60 years of age

- Initiation of HRT in women over 60 for menopausal symptoms should only be considered after careful individual assessment of risks and benefits of taking HRT
- Oral HRT is associated with slightly increased risk of stroke in women over 60, therefore it should be avoided in this cohort of patients
- Low dose transdermal oestrogen with micronised progesterone should be considered in women over 60
- Evidence from the Cochrane data-analysis as well as the long-term follow-up data from the Women's Health Initiative (WHI) showed no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who initiated HRT more than 10 years after the menopause
- Women who have started HRT in perimenopausal or menopausal period can continue with this treatment in their 60s, depending on the benefit and risk analysis, and can make an informed choice of when to stop HRT. Women on oral HRT should be swapped to transdermal formulation at 60
- Premarin® and Premique Low Dose® contain conjugated equine oestrogen (CEE) which is thrombogenic and are not recommended for women over 60 years of age
- If risk factors for CVD/VTE are present refer to menopause specialist

5.3 Venous thromboembolism

- Oral HRT is associated with an increased risk of VTE
- Transdermal HRT preparations (oestrogen only if no uterus, or oestrogen combined with oral micronised progesterone, or transdermal oestrogen and norethisterone in combined patch if uterus is present) should be considered in women who are already at increased risk of VTE, including those with a BMI over 30kg/m^2.
- Dydrogesterone is also associated with lower risk of VTE, however oral HRT containing estradiol combined with dydrogesterone (e.g., Femoston® range) or progesterone (Bijuve®) should be avoided in patients who are already at increased risk of VTE, including those with a BMI over 30 kg/m2
- Consider Mirena® and transdermal oestrogen as a choice in women with increased risk of VTE. Faculty of Sexual and Reproductive Healthcare (FSRH) states that current evidence suggests there is little or no increased risk of VTE with levonorgestrel intrauterine system
- Menopausal women at high risk of VTE (e.g., those with a strong family history of VTE or a hereditary thrombophilia) should be referred to a haematologist for assessment before considering HRT and or to menopause specialist

5.4 Diabetes mellitus

- Women with diabetes should be treated with HRT according to their risk of CVD and their BMI. They should also be managed with lifestyle intervention and a combined focus on metabolic, cardiovascular and bone health
- Women with BMI >30 and at low to moderate risk of CVD can be treated with transdermal oestradiol after performing a benefit versus risk assessment
- Women with BMI<30, with low risk of CVD, should be offered oral oestrogen HRT (only women <60) or transdermal oestrogen (no age restriction) depending on patient's choice. However oral estradiol is better for improving insulin sensitivity compared with transdermal estradiol

- If addition of progestogen is required in women with uterus, the one with neutral effects on glucose metabolism should be used, such as oral micronised progesterone or dydrogesterone (available only as combined oral preparation), or transdermal norethisterone (available only as combined transdermal preparation). Oral androgenic progestogens such as oral norethisterone and medroxyprogesterone should be avoided in diabetes.
- Patients with high risk factors for CVD, end organ damage from diabetes or established CVD should be either offered alternative treatment to HRT or to be referred to the menopause specialist

5.5 Migraine with and without aura

- Fluctuating oestrogen levels and menstrual disorders are associated with increased migraine prevalence during the perimenopause
- Migraines with aura is not a contraindication for HRT, however transdermal HRT is recommended
- Consider the lowest dose of transdermal oestrogen HRT that effectively controls vasomotor symptoms
- Where progestogen is required, continuous delivery is recommended with preparations such as:
  - levonorgestrel intrauterine system (Mirena®)
  - transdermal norethisterone (as in combined patches)
  - oral micronised progesterone
- Refer to BMS: Migraine and HRT for further information

5.6 Multiple factors for CVD

- Refer to menopause specialist
- See NICE CVD risk assessment and management for further information

5.7 Hyperlipidaemia and hypertriglyceridemia

- Oral oestrogen has more favourable effects on lipid profile in comparison to transdermal oestrogen (reduces total cholesterol and LDL-C, and increases HDL-C), however oral oestrogen is associated with increase in serum triglycerides
- Androgenic progestins including norethisterone and medroxyprogesterone attenuate beneficial effect of oestrogen on HDL-C
- In patients with hypertriglyceridemia transdermal oestrogen should be offered and oral oestrogen should be avoided
- In patients with CVS/VTE risks and high level of triglycerides, BMS recommends transdermal oestrogen combined with progestogen such as oral micronised progesterone which has neutral effect on lipid metabolism. Other options include levonorgestrel IUS Mirena® combined with transdermal oestrogen or combined estradiol with norethisterone patches due to their neutral effect on triglycerides and lipid profiles, however these treatment options do not increase HDL-C
- In patients under 60 with low CVS /VTE risks and normal triglyceride level oral oestrogen with dydrogesterone or oral oestrogen with micronised progesterone (Bijuve®) can be considered as dydrogesterone and micronised progesterone do not negate the beneficial effects of oral oestrogen on HDL-C.

5.8 Hypertension

- Offer transdermal HRT (and treat high blood pressure)

5.9 Porphyria cutanea tarda (PCT)

- NICE recommends that HRT in patients with PCT should be used with caution. Oestrogens are implicated in the pathogenesis of PCT, and they should not be prescribed until condition has been fully treated and the patient is in complete remission. After treatment, HRT might be used with caution. All patients with PCT should be referred to the menopause specialist or/and porphyria specialist

5.10 History of endometrial hyperplasia

- Patients with a history of endometrial hyperplasia should be referred to the menopause specialist

5.11 Increased risk of breast cancer

- Patients with a family history suggestive of a moderate to high risk of breast cancer should be referred to the family history clinic to assess their risk (see NICE CG164 section 1.3 for recommendations for referral to secondary care)
- Patients with already confirmed a moderate to high risk of breast cancer due to family history and/or abnormal biopsy please refer to table 6 for further information

6. Benefits of HRT[1,2,6,10,18,19,20,32]

- Benefits and risks need to be assessed individually in every case
- For most women, HRT is a safe and appropriate option, in conjunction with improving lifestyle, particularly in women under 60 years of age

6.1 Control of menopausal symptoms

- Reduction in and control of menopausal symptoms (including genitourinary syndrome of menopause (GSM)). Local (vaginal) oestrogen can be added to systemic HRT if required to treat GSM.
- Improvement of quality of life and sex drive

6.2 Osteoporosis

- Protection against fragility fracture. This benefit is maintained during treatment; however, it decreases once treatment stops
- Consider prescribing HRT to younger postmenopausal women to reduce the risk of fragility fractures and for the relief of menopausal symptoms
- BMS advises that HRT can be considered as a treatment option for osteoporosis in postmenopausal women under 60 who do not have risk factors for breast cancer, heart disease, stroke, or thrombosis
- HRT provides bone protection is women with POI or early menopause

6.3 Cardiovascular disease (CVD)

- NICE advises that in women with POI or early menopause starting hormonal treatment (either with HRT or a combined hormonal contraceptive) and continuing it until the age of natural menopause (unless contraindicated) reduces the risk of CVD

- In women with POI or early menopause, HRT may have a beneficial effect on blood pressure when compared with a combined hormonal contraceptive. HRT is also metabolic friendly when compared with a combined hormonal contraceptive
- Evidence from the Cochrane data-analysis as well as the long-term follow-up data from the Women's Health Initiative (WHI) showed no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who initiated HRT more than 10 years after the menopause
- Timing hypothesis: if HRT initiated before the age of 60 or within 10 years of the menopause is likely to be associated with a reduction in coronary heart disease and cardiovascular mortality
- HRT does not increase CVD risk when started in women aged under 60
- HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease
- Transdermal HRT is recommended if over 60. Oral HRT is avoided as it is associated with slight increased risk of stroke over age 60

6.4 Cognitive decline

- HRT may reduce risk of cognitive decline in women with POI

7. Risk of HRT[1,2,3,12,13,21,22,23,24,25,26,27]

7.1 Breast cancer

- The risk of breast cancer is increased during use of all types of HRT except vaginal oestrogens, (MHRA drug-safety-update/hormone-replacement-therapy-Aug 2019). However, for most women this risk is small and needs to be assessed individually in each case
- NICE guideline concluded the following:
  - the baseline risk of breast cancer for women around menopausal age varies from one woman to another according to the presence of underlying risk factors
  - HRT with oestrogen alone is associated with little or no change in risk of breast cancer
  - HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer
  - any increase in the risk of breast cancer is related to treatment duration (is not dose dependant) and reduces after stopping HRT (over several years)
- BMS advises that risk of breast cancer is duration dependant and the risk of breast cancer caused by exposure to HRT is established as less than the postmenopausal lifestyle risk factors for breast cancer such as obesity and excessive (2 units of alcohol or more per day) alcohol intake. This should be taken into context of overall benefits. See BMS/Women's Health Concern chart on understanding the risk of breast cancer for further details and BMS Fast Facts HRT and Breast Cancer Risk.
- BMS states there is no significant difference in overall breast cancer mortality with combined HRT and a lower breast cancer mortality with oestrogen only HRT (BMS refers to long-term data from Women's Health Initiative (WHI) study which was published in The Journal of the American Medical Association (JAMA) 2020)
- BMS advises that continuous combined HRT is associated with a slightly higher risk than sequential combined HRT and the risk depends on the type of progestogen
- HRT containing dydrogesterone and micronised progesterone has a lower risk of invasive breast cancer compared with other progestogens for short term use under 5 years and there is an increase in the risk with long term use >5 years

- There is possible increased risk of breast cancer in users of levonorgestrel intrauterine system (used as part of HRT), however only limited safety data is currently available and further research in this area is required
- In women with POI (under 40) or early menopause (40-45), years of HRT exposure should be counted from the age of 50 and not when the HRT was commenced

7.2 Venous thromboembolism (VTE)

- Risk of VTE is higher with oral HRT (2-fold risk) and the occurrence of such event is more likely in the first year of HRT than later
- The risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk
- The main cause of increased risk of HRT is the oral oestrogen component,
- NICE states that the progestogen component of HRT may also influence the risk which may be greater with androgenic synthetic progestogens or progestins (such as oral norethisterone and medroxyprogesterone) than natural progesterone (see section 5.3 for further information)
- Consideration should be given to prescribing transdermal oestrogen in patients with increased risk of VTE and using dydrogesterone and micronised progesterone as these are unlikely to increase the risk compared with other progestogens. However, in UK, dydrogesterone is only available as an oral preparation combined with oestradiol therefore should be avoided in women at high risk of VTE.
- Transdermal estradiol and norethisterone in the combined patch do not increase risk of VTE
- Use of estradiol vaginal preparations is not associated with VTE risk

7.3 Ovarian cancer

- The risk of ovarian cancer whilst taking HRT was established as: 1 extra case per 1000 users after 5 years of treatment with HRT and 1 extra death per 1700 users. The risk disappears within a few years of stopping HRT

8. Principles of prescribing HRT[1,2,28]

8.1 Assessment prior commencement of the HRT treatment in menopause, perimenopause or POI should include:

- Review of menopausal symptoms including their nature, frequency, duration, time of day, their severity and impact on quality of life
- Review of local vulvovaginal symptoms
- Assess of the need for ongoing or future contraception (refer to section 15)
- Family history including early menopause or POI, cardiovascular disease (CVD), VTE, hormone dependant cancers (including breast, ovarian, endometrial, colon), osteoporosis
- Medical history or risk of CVD (see NICE on CVD risk assessment), hypertension (HPT) (see NICE on HPT), diabetes mellitus type 2 (see NICE on diabetes type 2), VTE (see NICE on DVT /PE), stroke (see NICE on Stroke and TIA), hormone dependent cancer including breast, ovarian endometrial and colon, previous medical or surgical treatment including chemotherapy, radiotherapy, hysterectomy and /or bilateral oophorectomy, bone health and risk of osteoporosis

- Medical history of migraines with or without aura (see section 5.3 for further information)
- Drug history including medicines bought over the counter (OTC) and herbal products. If HRT treatment already trialled, review its effectiveness and tolerability.
- Patient lifestyle factors such as alcohol intake, smoking status, exercising, diet
- Check patient blood pressure (BP) and body mass index (BMI)

8.2 Choice of HRT, route of administration, formulation, and dosing

- Provide information about menopause, perimenopause or POI and treatment options (including non-HRT therapy) to help women make informed, individualised decisions about management
- Provide patients with information leaflets on menopause and HRT (e.g., https://patient.info/womens-health/menopause , https://patient.info/womens-health/menopause/hormone-replacement-therapy-hrt) and inform patients about websites dedicated to menopause including www.thebms.org.uk , www.menopausematters.co.uk, www.womens-health-concern.org , www.daisynetwork.org
- Provide information and advice on lifestyle measures for symptom relief (including smoking cessation, weight management, reduction in alcohol intake, healthy diet, and adequate vitamin D supplementation)
- Offer choice of HRT preparation, based on patient age, symptoms, and co-morbidities, after discussing potential risks, benefits, adverse effects, and contraindications
- HRT is available as oral and transdermal preparations
- In general oestrogen-only preparations are given to women without uterus and combined oestrogen and progestogen preparations are given to women with an intact uterus. See section 3.5 about recommended treatment options for women without uterus and severe endometriosis
- Transdermal preparations might be appropriate in women with:
    - Persistent troublesome symptoms or/and adverse effects (including nausea, headache, breast tenderness) with oral treatment
    - A history or increased risk of VTE
    - Cardiovascular risk factors, such as obesity (BMI>30), uncontrolled hypertension, or hypertriglyceridemia
    - Taking hepatic enzyme-inducing drug treatment e.g., carbamazepine, lamotrigine (refer to BNF for drug interactions). Transdermal formulation bypasses the liver.
    - Taking oral levothyroxine (, for further information see NICE on Hypothyroidism)
    - A gastrointestinal disorder that may affect absorption of oral treatment (e.g., Crohn's disease)
    - A history of migraines (refer to BMS fact sheet on HRT and migraines for further information)
    - A history of gallbladder disease
    - Lactose sensitivity (most HRT oral preparations contain lactose)

- Transdermal preparations are available as gel (oestrogen only), patch (oestrogen only or combined oestrogen and progestogen), or spray (oestrogen only)
- Patches have the advantage of needing to be changed usually twice weekly, whereas gels usually need to be administered daily. The disadvantages of patches are that they can fall off, may cause skin irritation and can be unsightly
- If women are using combined HRT, the progestogen component can be given separately as an oral tablet or as the levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena®) or in the combined patch
- In women age >60, consider transdermal HRT and start at low dose. Review patient response after 3 months and adjust the treatment dosing if required.

9. Oestrogens [2,28,29,30,31,32,33,34,35,36,37]

9.1 Choice of HRT products containing oestrogens

- There are 3 types of oestrogens available for HRT .17β estradiol (E2) is body identical (the preferred oestrogen both alone and in combination HRT preparations), estradiol valerate and conjugated equine estrogen (CEE).
- Conjugated equine oestrogen (CEE) such as Premarin® is thrombogenic and can cause idiosyncratic hypertension. It is only prescribed for women who are already taking very low dose of 0.3 mg with no side effects and should be avoided in over 60s.

Table 1- Oestrogen products (based on BMS HRT practical prescribing which was adapted to align with the GMMMG Joint Formulary)

Oestrogen	Available formulation	
	Systemic	**Low-dose vaginal oestrogens for urogenital symptoms**
Estradiol	0.5mg (combined only)/ 1mg / 2mg oral	10mcg vaginal tablets Vagirux®
	25mcg / 37.5mcg / 50mcg / 75mcg / 100 mcg transdermal patches	7.5mcg vaginal ring Estring®
	0.06% transdermal gel, Oestrogel®	No topical vaginal formulations available
	0.5mg / 1mg transdermal gel Sandrena® sachets	No topical vaginal formulations available
	1.53 mg/metered dose transdermal spray Lenzetto®	No topical vaginal formulations available
Estriol	No systemic formulations available	0.1% vaginal cream, Ovestin®
		30mcg vaginal pessary, Imvaggis®
Conjugated equine oestrogens	0.3mg oral, Premarin® (available also as combined Premique Low Dose®)	No topical vaginal formulations available

9.2 Prescribing of oestrogens

- Choice of oestrogen HRT should depend on patient preferences
- Oral preparations are suitable in ‘low risk patients’ and under 60 years of age
- Transdermally administered oestrogen avoids first-pass metabolism. For further information on transdermal preparations please see section 8.2, see also **Table 2** below for estradiol equivalent doses depending on formulation
- For choice of oestrogen products see **Table1** above
- Dose depends on patient age, severity of symptoms, co-morbidities
- Women with early menopause or POI may require high oestrogen doses for symptom relief, whereas older women may need to start or be maintained on a lower oestrogen dose
- Oestrogen HRT should be started with lower doses and titrated up to relieve symptoms.
- BMS recommends that if HRT is to be used in women over 60 years of age, lower doses should be started, preferably with a transdermal route of estradiol administration

Table 2 - Estradiol equivalent doses* (based on BMS HRT practical prescribing)

Dose of estradiol	**Estradiol tablet (**1mg, 2mg**) Daily**	**Estradiol patch (**25, 37.5, 50, 75,100 mcg**) Twice a week**	**Estradiol gel pump, Oestrogel® (0.06%) (**1 pump contains 64 metered doses**) Daily**	**Estradiol gel sachets, Sandrena® (0.5 mg/1 mg) Daily**	**Estradiol transdermal spray, Lenzetto® (1.53 mg/metered dose) Daily**
Ultra low dose	0.5mg (only available in combined HRT)	half of 25mcg patch (off licence)	half of 1 pump (0.375mg)	half of 0.5mg sachet - 0.25mg	1 spray provides 21mcg/day mean serum estradiol level after 12 weeks of therapy**
Low dose	1mg	25mcg	1 pump (0.75mg)	0.5mg	2 sprays provide 29mcg/day mean serum estradiol level after 12 weeks of therapy**
Medium dose	2mg	50mcg	2 pumps (1.5mg)	1-1.5mg	3 sprays provide 40mcg/day mean serum estradiol level after 12 weeks of therapy**
High dose	3-4mg (off label) (It is recommended to start at lower 2mg dose and increase further if needed)	75-100mcg, (It is recommended to start at lower dose at 50mcg and then increase further if needed)	3-4 pumps (2.25-3mg) (off label) (It is recommended to start with 2 pumps and then increase the dose further if needed)	2-3mg (off label) (It is recommended to start with lower dose and then increase further if needed)	No equivalent dose available

* The dose equivalents are subject to significant individual variations in absorption and metabolism

** Data from study by Buster J.E. et al.

9.3 Monitoring of treatment with estradiol (E2) in Primary Care

- If poor response to oral E2 after 3 months of therapy the dose can be increased (rule out other causes of reduced efficacy such as drug interactions, malabsorption).
- Consider changing to transdermal preparation if insufficient response with oral treatment continues and further increase in dose
- Symptom control is the most appropriate way to assess HRT efficacy however if inadequate symptom control observed with transdermal HRT consider testing for serum E2 levels
- If inadequate response observed with transdermal HRT, in spite of increase in dose, consider checking serum E2 levels. Adequate serum E2 level is around 200pmol/L (200 - 400 pmol/L in POI)

- If low levels of serum E2 with transdermal E2 consider changing to a different transdermal formulation e.g., patch to spray or gel and etc
- If serum E2 are above normal range and patient has poor symptom control rule out other causes such as compliance, patch not sticking well, absorption problems, drug interaction and consider an alternative diagnosis and refer to endocrine specialist.

9.4 Oestrogen side effects and their management

- Most of the side effects resolve within 3-6 months on the HRT, however if not settled, treatment may require to be altered (e.g., by reducing the dose or formulation, or the HRT product)
- Most common side effects include:
  - Fluid retention
  - Breast tenderness
  - Bloating
  - Leg cramps -
  - Nausea/dyspepsia
  - Headaches
  - Vaginal bleeding
- More information of side effects can be found here https://thebms.org.uk/wp-content/uploads/2022/05/03-BMS-TfC-HRT-Practical-Prescribing-02A-MAY2022.pdf

9.5 Low-dose vaginal oestrogens for urogenital symptoms (genitourinary syndrome of menopause)

- Offer low-dose vaginal oestrogen and continue treatment for as long as needed to relieve symptoms (some women on systemic HRT may also benefit from additional low-dose vaginal oestrogen)
- There is minimal systemic absorption and therefore risks associated with HRT are not applicable when using low-dose vaginal oestrogen
- Patients in whom systemic HRT is contraindicated (including patients on treatment for breast cancer) should be referred to menopause specialist
- In women with a personal history of breast cancer vaginal dryness should initially be managed with vaginal lubricants or moisturisers. If these occur ineffective patients should be referred to the menopause specialist/breast cancer specialist
- Estriol vaginal cream can also be used externally on vulva if required in addition to vaginal treatment
- Estriol vaginal cream or pessary is used for the prophylaxis of recurrent urinary-tract infection in postmenopausal women, but is not licensed for this indication
- It can take 6 - 12 weeks, from the start of treatment with low-dose vaginal oestrogen, to observe improvement in symptoms
- Estriol is a weaker form of oestrogen than estradiol
- Treatment with low-dose oestrogen should be individualised
- Treatment options available in the GM formulary are listed below:
  - estriol 0.1% vaginal cream Ovestin®,
  - estradiol 10mcg vaginal tablet Vagirux®
  - estriol 30mcg vaginal pessary Imvaggis® (some patients find pessaries more moisturising),

- estradiol 7.5mcg/24hrs vaginal ring Estring® (reserved for patients with limited dexterity who find it difficult to insert pessaries or apply cream; Estring® can be worn for 3 months and can be inserted by clinician)

- If a low-dose oestrogen preparations do not relieve symptoms sufficiently, consider seeking specialist advice about increasing the dose
- Advise that vaginal moisturisers and lubricants can be used alone or in addition to vaginal oestrogen preparations.
- From September 2022 there is a low oestrogen vaginal product, Gina® estradiol 10mcg vaginal tablet, which can be purchased by women without prescription (P med). Further information can be found on the BMS website

10. Progestogens[2,3,5,12,13,21,25,26,29,31,38,39,40,41,42,43,44]

- All women with an intact uterus need a progestogen to be added to their oestrogen to prevent endometrial hyperplasia,
- The progestogens most commonly used in combined oral HRT include:
  - progesterone (body identical) and its synthetic analogues dydrogesterone and medroxyprogesterone
  - testosterone synthetic analogue norethisterone
  - levonorgestrel is the active isomer of norgestrel. Norgestrel is a synthetic testosterone analogue
- Women vary in their tolerance to progestogens, and changing the progestogen component of combined HRT may be needed if progestogenic adverse effects occur
- Women with perimenopausal depression are often intolerant to progestogens, with many women reporting mood changes during the progestogenic component of combined sequential and continuous HRT. Micronised progesterone and dydrogesterone are associated with fewer side-effects than the more androgenic progestogens which are best avoided in such women

Table 4 - Progestogen products (based on BMS HRT practical prescribing)

Table 3 - Progestogen dosing		
All progestogens to be prescribed in combination with oestrogen products		
Progestogen	**Sequential**	**Continuous Combined**
Utrogestan® micronised progesterone 100mg oral capsules	200mg for last 12-14 days of each 28 days cycle (at bedtime) (14 days use is off label)	100mg capsule daily (at bedtime) (off label) (licensed use is 100mg capsule daily on days 1-25 of 28 day cycle)
Provera® medroxyprogesterone 2.5, 5,10 mg oral tablets	10 mg for 12-14 days every month	2.5 or 5mg daily
Norethisterone oral tablets 5mg	5 mg for 12-14 days every month (unlicensed)	3 tablets daily of 350mcg Noriday® (unlicensed) or 5mg daily if lower dose unavailable (unlicensed)
Mirena® IUS levonorgestrel 20mcg/24 hrs	N/A	Can be used for 5 years (off label)

Progestogen	**Available formulation**
Micronised progesterone	100mg oral capsules, Utrogestan®
Dydrogesterone	Combined oral and transdermal formulations
Norethisterone	Combined oral and transdermal formulations
	5mg tablets or 350mcg tablets

Levonorgestrel	IUS, Mirena®
Medroxyprogesterone acetate	Combined oral, Premique® Low Dose
	2.5mg, 5mg, 10mg tablets, Provera®

10.1 Progestogens side effects and risk comparison

Table 5 – Progestogens, used as HRT, side effects and risk comparison

Type of progestogen	Androgenic activity	Metabolic effects on lipids and insulin	Risk of VTE	Breast cancer risk
Micronised progesterone (Utrogestan ® oral capsules) *	Not androgenic (doesn't bind to androgenic receptors)	Neutral effect on lipid profile and glucose metabolism	Lower than other progestogens	Lower than androgenic progestogens. See section 7.1 for further details
Dydrogesterone (only available as combined HRT e.g., Femoston® oral tablets)	Less androgenic than norethisterone	Neutral effect on lipid profile and glucose metabolism	Lower than other progestogens	Lower than other androgenic progestogens. See section 7.1 for further details
Norethisterone (available as oral and transdermal formulation)	Androgenic	Oral formulation-unfriendly for glucose, HDL-C and triglycerides Transdermal formulation-neutral on glucose metabolism and triglycerides	Higher than micronised progesterone and dydrogesterone	Higher than dydrogesterone and micronised progesterone
Medroxyprogesterone acetate (only available as oral formulation)	Less androgenic than norethisterone or levonorgestrel	Unfriendly	Higher than micronised progesterone and dydrogesterone	Higher than dydrogesterone and micronised progesterone
Levonorgestrel intrauterine system (Mirena®)	Mirena provides endometrial protection locally, resulting in low systemic levels of levonorgestrel. Lower androgenic effect than oral levonorgestrel.	Neutral effect on lipid profile and triglycerides	As per current evidence there is little or no increased risk of VTE associated with Mirena®	Possible increased risk of breast cancer however only limited safety data is currently available

*BMS advise that women who do not tolerate oral progesterone intake, vaginal administration of oral micronised progesterone preparations (Utrogestan® 100 mg capsules licences for oral use) can be considered on exceptional basis. This will be off license of the products and there is no available evidence on the absorption kinetics of progesterone

preparations intended for oral intake when administered vaginally. Such intake should follow the same doses recommended with oral intake. See BMS Progestogens and endometrial protection for further details.

11. Tibolone[29,45,46,47]

- Tibolone is a CCHRT. It combines oestrogenic and progestogenic activity with weak androgenic activity
- It can be used in women with an intact uterus who have had no bleeding for more than one year
- It might be helpful in improving sexual drive in menopausal women due to its androgenic effects and can be used in women with endometriosis. Tibolone has a lower risk of breast cancer compared with other combined HRT as was reported in the Million Women Study. Unlike conventional HRT, tibolone has a limited effect on mammographic density. Tibolone has a higher risk of stroke as was reported in the long-term intervention on fractures with tibolone (LIFT) study

12. HRT Treatment Options[1,2,3,32,48,49]

Before starting HRT:

•Review menopausal symptoms including their nature, frequency, duration, time of day, their severity and impact on quality of life

•Provide patients with information leaflets on menopause and HRT (e.g., https://patient.info/womens-health/menopause , https://patient.info/womens-health/menopause/hormone-replacement-therapy-hrt) and inform patients about websites dedicated to menopause including www.thebms.org.uk , www.menopausematters.co.uk, www.womens-health-concern.org , www.daisynetwork.co.uk

•Provide information and advice on lifestyle measures for symptom relief (including smoking cessation, weight management, reduction in alcohol intake, healthy diet) and adequate vitamin D and calcium supplementation

•Offer individualised choice of HRT preparation, based on patient age, symptoms and co-morbidities, after discussing potential risks, benefits, adverse effects and contraindications. Women ≥60 years of age should be offered transdermal formulation first line.

HRT for menopause management

Post hysterectomy. Diagnosis based on symptoms. For prescribing in subtotal hysterectomy and severe endometriosis **see sections 3.3 and 3.5**	**Intact uterus**		**Vaginal symptoms**
	Perimenopausal Last menstrual period <12 months ago or irregular periods, and vasomotor symptoms	**Postmenopausal** Last menstrual period >12 months ago and not using hormonal contraception	**Low-dose vaginal oestrogen (estriol and estradiol). See section 9.5** for further information
Oestrogen only HRT	**Sequential combined HRT**	**Continuous combined HRT**	
1.Oral treatment options	**1.Oral treatment options**	**1.Oral treatment options**	
•Elleste-Solo®1mg, 2mg tablets-daily •Premarin® 0.3mg tablets -to be prescribed only for patients already taking it and well tolerating this therapy	•Femoston 1/10, 2/10 tablets-daily •Elleste Duet® 1mg, 2mg tablets-daily	•Femoston-conti® 0.5mg,1mg tablets-daily •Bijuve® 1mg/100mg capsule - daily •Elleste Duet Conti® 2mg; Kliofem® 2mg; Kliovance® 1mg tablets-daily •Premique Low Dose® 0.3/1.5mg tablets to be prescribed only in women already taking it and well tolerating this therapy	**Treatment options**
2.Transdermal treatment options	**2.Transdermal treatment options** •Evorel Sequi ® 50mcg patch -twice a week		•Ovestin® estriol 0.1% vaginal cream
•Evorel® 25, 50,75,100 mcg patch twice a week •Estradot® 25, 37.5, 50, 75, 100 mcg patch-twice a week, •Gel (Oestrogel® pump, Sandrena® sachets) •Spray (Lenzetto®). Gel and spray to be used daily.	**3.Transdermal /oral oestrogen plus levonorgestrel intrauterine system Mirena®**	•Tibolone 2.5mg tablets-daily (**see section 11** for further information)	•Vagirux® estradiol 10mcg vaginal tablet
	4.Transdermal/oral oestrogen plus oral progestogen (for progestesterone dosing see Table 3) •Utrogestan® progesterone 100mg capsules •Provera® medroxyprogesterone acetate 10mg tablets (unlicensed) •Norethisterone 5mg tablets (unlicensed)	**2.Transdermal treatment options** •Evorel Conti® 50mcg patch-twice a week **3.Transdermal /oral oestrogen plus levonorgestrel intrauterine system Mirena®** **4.Transdermal/oral oestrogen plus oral progestogen (for progestesterone dosing see Table 3)** •Utrogestan® 100mg progesterone capsules •Provera® medroxyprogesterone acetate 2.5mg,5mg tablets (unlicensed) •Norethisterone 5mg (unlicensed) or Noriday®3x350mcg tablets (unlicensed)	•Imvaggis® estriol 30mcg vaginal pessary •Estring® estradiol 7.5mcg vaginal ring - for patients with limited dexterity
Sequential Combined HRT (seq HRT with menstrual bleeding) to be changed to continuous combined HRT (CCHRT):1)at the age of 55; 2) after 1 year of seq HRT if the woman wishes to avoid a monthly withdrawal bleed. CCHRT is a "bleed-free" HRT, however in the 1st 6 months it can cause irregular vaginal bleeding which does not require investigations.			
Non-hormonal vaginal moisturisers/lubricants can be used alone or in addition to low-dose vaginal oestrogen.			

13. Follow up and discontinuation of HRT[1,2,50]

13.1 Review at 3 months

- Arrange to review the woman after 3 months if HRT has recently been started or changed
- Assess control of symptoms and adverse effects and offer to adjust the HRT dose or preparation if needed
- Check bleeding pattern. Explain women with a uterus that unscheduled vaginal bleeding or spotting whilst on CCHRT or tibolone is common if it occurs during the first 4-6 months of treatment, however it should be reported if heavy bleeding occurs. This bleeding usually settles after 6 months. There might occur heavy or irregular bleeding with sequential HRT which should settle within 6 months.
- Indications for referral under 2-week wait:
  - Postmenopausal bleeding: bleeding 12 months after LMP
  - Abnormal bleeding on HRT more than 6 months after start or change of HRT (to be confirmed with local pathway if 2-week wait referral is required)
  - Vaginal bleeding persisting 6 weeks after stopping combined HRT
- Check BP and BMI
- Reinforce information and lifestyle advice
- Prescribe HRT for 3-6 months at a time (depending on shortages)

13.2 Review annually, unless there are clinical indications for an earlier review (such as treatment ineffectiveness, side effects or adverse events or changes in medical history or high risk cases)

- After '3 months review' the HRT treatments should be assessed at least annually
- Discuss benefits and risks of prescribed HRT

13.3 Duration of HRT therapy

- Therapy should be continued for as long as benefits outweigh any risks. No arbitrary time limit should be placed on duration of use of HRT and decision should be made on an individual basis
- Women with premature menopause or POI should take HRT up to the average age of the natural menopause (51 years in the UK), after which the need for ongoing HRT should be reassessed
- Vaginal oestrogen preparations may be required long term

13.4 Treatment discontinuation

- Treatment can be stopped immediately or can be gradually reduced. It makes no difference to long term symptoms
- If treatment is tapered down, reduce the daily dose (if possible), rather than dose frequency, for 3-6 months. Reducing dose frequency may lead to fluctuations in hormone levels.

14. Testosterone[2,47,51,52,53,54,55,56,57]

14.1 Role of testosterone

- Testosterone is an important female hormone
- It contributes to libido and sexual arousal, by increasing dopamine levels in the central nervous system.
- It maintains normal metabolic function, muscle and bone strength, urogenital health, mood, and cognitive function

14.2 Indications for testosterone therapy

- In women with induced medical or surgical menopause and in POI, testosterone production decreases abruptly by more than 50%
- Induced ovarian failure might be a result of interventions such as pelvic irradiation therapy, chemotherapy, surgical oophorectomy (including bilateral salpingo-oophorectomy)
- NICE recommends testosterone supplementation for postmenopausal women with low sexual desire causing distress, if HRT alone is not effective. The treatment can be given to women with menopause (including medical and surgical menopause), post-menopause and in POI
- Women should be assessed for hypoactive sexual desire disorder (HSDD). Diagnosis for HSDD (persistent lack of desire) should be based on the assessment via Decreases Sexual Desire Screening tool (DSDS) along with a full biopsychosocial assessment
- Testosterone could be initiated after full biophysical evaluation and management of other conditions predisposing to low sexual desire such as dyspareunia (including genitourinary syndrome and vulvovaginal atrophy), fatigue secondary to vasomotor symptoms, anaemia, thyroid disease, anxiety, depression, medication side effects, and relationship issue
- Due to lack of evidence testosterone is not recommended to be used on its own for mood, cognition, muscle, and bone strength improvement

14.3 Contraindications to testosterone therapy

- Pregnancy, breast feeding
- Active liver disease
- History of hormone sensitive breast cancer
- Upper normal or high baseline total testosterone levels
- Competitive athletes

14.4 Investigations prior commencement of the treatment with testosterone and monitoring of the therapy

- Consider testing baseline serum total testosterone and sex hormone binding globulin (SHBG). Baseline levels are performed to ensure testosterone levels are not raised to supraphysiological levels at the start of the treatment with testosterone
- Repeat above blood tests at 8-12 weeks after starting treatment and 6-monthly thereafter. There is no blood level that is a treatment goal for testosterone therapy, however levels should be monitored to ensure they are in pre-menopausal reference range (check normal range for the local laboratory)
- On treatment - serum testosterone should be maintained in the pre-menopausal reference range. Free testosterone level is not recommended as correlation with biological activity of testosterone has not been established.

14.5 Prescribing advice and product choice

- Testosterone therapy can be initiated in primary care following specialist recommendation (testosterone GMMMG RAG status is 'Green after specialist advice', see GMMMG RAG for further information)
- If patient takes oral HRT and experiences low sexual desire, switch from oral formulation to transdermal oestrogen HRT before considering testosterone therapy. Transdermal preparations have minimal effect on SHBG, therefore can improve patient sexual function
- In menopausal women under 60 years with intact uterus (LMP>12 months) and low sexual desire can consider treatment with tibolone
- If HRT is not effective in managing symptoms of HSDD, Primary Care prescribers should check the baseline serum total testosterone and SHBG levels, and seek advice from the menopause specialist on prescribing of testosterone
- Primary Care prescribers should follow the specialist advice on appropriate selection and dosing of testosterone preparations in postmenopausal women
- There are no licensed testosterone preparations available to be used in menopausal women. Therefore, preparations licensed to be used in men (gels) are prescribed in 'female' doses (usually 1/8 - 1/10 of the male dose depending on the preparation used) as long as they meet the criteria proposed by General Medical Council (GMC) and Medicines and Healthcare Products Regulatory Agency (MHRA) of prescribing a drug off label or out of licence.
- Prior to commencement of treatment with testosterone patient should be informed that treatment with testosterone in menopausal women with low sexual desire is an unlicensed therapy
- Testosterone products used out of licence in menopausal women include:
  - Testogel® (new formulation- 2.5g sachets containing 40.5mg testosterone): Starting dose 1/8 of a sachet/day = approx. 5mg/day i.e., each sachet should last 8 days
  - Testogel® (old formulation - 1% testosterone gel in 5.0 g sachets containing 50 mg testosterone): Starting dose 1/10 of a sachet/day = 5 mg/day i.e., each sachet should last 10 days
  - Tostran® (2% testosterone gel in a canister containing 60g): Starting dose 1 metered pump of 0.5g = 10mg on alternate days – each canister should last 240 days.
  - Testim® (1% testosterone gel in 5ml tubes): Starting dose 0.5ml (5mg) per day making each tube last for 10 days.
  - For further information see GMMMG Joint Formulary section 6.4.2, BNF online :Testosterone and BMS: testosterone replacement in menopause
- If there is no adequate response observed with testosterone after 3-6 month, consider stopping the treatment
- If there is improvement in symptoms, women should continue treatment and have an annual re-evaluation of weighing up benefits and risks of continuing treatment

14.6 Testosterone side effects

- Patient should be counselled about side effects due to testosterone therapy (these are usually a consequence of inappropriate dosing)
- Testosterone side effects include:

- Increased hair growth at site of application (occasional problem) – spread more thinly, vary site of application
- Acne and greasy skin (uncommon)
- Generalised hirsutism (uncommon)
- Alopecia, male pattern hair loss (uncommon)
- Deepening of voice (rare, irreversible and the treatment should be stopped immediately)
- Enlarged clitoris (rare, irreversible)

- The above side effects could be managed by reducing testosterone dose or the treatment should be stopped, and advice sought from the specialist

15. Managing contraception in women on HRT[7,58,59]

- Hormonal contraception (levonorgestrel IUS (LNG-IUS) (Mirena®), implant (IMP), progesterone only pill (POP), progestogen only injectable are contraceptive options which can be used alongside HRT
- Current guidance recommends that contraception can be stopped 2 years after last period if woman is less than 50 years old and 1 year after last period if woman is over 50 years old
- The Faculty of Sexual and Reproductive Healthcare (FSRH) supports extended use of LNG-IUS Mirena® for contraception until the age of 55 if inserted at age 45 or over. This is off label use of Mirena® as per product license
- The FSRH, RCOG and BMS support extended use of Mirena® as part of HRT for endometrial protection to 5 years. This is also off label use of Mirena® because as per product licence it should be removed after 4 years of use
- Women on progesterone only contraception (IMP, POP and LNG-IUS) could stop the treatment at the age of 55 when natural loss of fertility can be assumed for most women. However, if a woman over 50 with amenorrhoea would like to stop the contraception sooner, FSH level can be checked. IF FSH level is over 30IU/L the IMP, POP and LNG-IUS can be stopped after 1 more year. IF FSH level is less than 30IU/L then the method should be continued and FSH checked again in 1 year. If patient is already taking HRT, this should be stopped for at least 6 weeks to measure FSH levels
- Consider stopping combined hormonal contraception at the age of 50 and switch to either non-hormonal method or IMP, POP and LNG-IUS, then follow appropriate advice (see above)
- If woman uses progestogen-only injectable contraception, consider switching to alternative methods at the age of 50
- In general, all women could cease contraception at the age of 55, however if a woman aged 55 or over would like to continue a particular method, benefits and risks should be discussed and then decision on continuation could be made
- Women with POI need to use contraception till age 55, if they do not wish to be pregnant as 5-10% of these women can ovulate and get pregnant
- Do not test FSH in woman on HRT or combined hormonal contraception
- Women on sequential combined HRT require contraceptive protection until age of 55

- Continuous combined HRT is usually started when a woman has no periods for 12 months, and do not need contraception

16. HRT and Covid 19 infection[60]

- Covid 19 infection is associated with increased thrombotic risk, therefore consider assessment of the VTE risk
- If patient is asymptomatic can continue with HRT whether oral or transdermal
- If patient is hospitalised or suffers from severe infection advice to be taken from treating physician and oral HRT must be stopped. Consideration may be given to swapping for transdermal HRT, but is not mandatory
- For further information see BMS Reflections and recommendations on the COVID-19 pandemic

17. Indications for referral to the specialist[2,61,62,63,64]

17.1 Red flag symptoms for 2-week urgent cancer referral to gynaecology clinic

- Post-menopausal bleeding (unexplained bleeding more than 12 months after LMP)
- Abnormal bleeding on HRT more than 6 months after start or change of HRT (check with local pathway if 2 weeks wait referral is required)
- Vaginal bleeding persisting 6 weeks after stopping combined HRT

17.2 Table 6 - non-urgent referral

Indications for referral	Where to refer a patient	Investigations required to be performed for the referral
Abnormal bleeding whilst on HRT persisting beyond 6 months On sequential HRT •change in withdrawal bleed pattern •heavy bleed /or break through bleeding persisting beyond 6 months (not usually indication for 2 weeks wait) On CCHRT •breakthrough bleed 6 months after starting •bleed after a period of amenorrhoea	Refer to gynaecology one stop clinic. 2 weeks wait for bleeding on CCHRT. (check with local gynaecology one stop clinic on pathway for referral)	Initial investigations of the woman with unscheduled bleeding on HRT include: a pelvic examination; vulval examination for signs of vulval conditions such as urogenital atrophy, lichen sclerosus/planus or vulval cancer; speculum examination to rule out cervical polyps or cervical cancer and to obtain a cervical smear test if indicated/due as well as rule out STI if the history suggests this. Refer for pelvic scan. Further endometrial evaluation is indicated if the ET is > 5mm in accordance with local protocols and national guidance
Menopausal symptoms unresponsive to trials with 2-3 different types of HRT	Refer to menopause specialist	Include HRT regimens tried within the referral letter
Medical history/family history of DVT /PE	Refer to menopause specialist	Include details of anti-coagulant history within the referral letter. Perform thrombophilia screen prior to referral after discussing with haematologist

Premature ovarian insufficiency: **r**efer if under 30 years and 30-40 years if not confident in treating	Refer to menopause specialist	FSH/LH (2 levels done 6 weeks apart >30IU), TFT, thyroid peroxidase antibodies, coeliac screen, baseline DEXA scan
Complex medical problems; history of CVD/stroke/multiple risk factors for CVD such as age/DM/hyperlipidaemia, obesity/ hypertension etc	Refer to menopause specialist	Include correspondence from secondary care about stroke/CVD etc, within the referral letter
Safety concerns about HRT for patients with breast abnormal biopsy	Refer to breast cancer specialist and menopause specialist	
Safety concerns about HRT for patients with VTE/CVS risks or other rare conditions	Refer to menopause specialist	
Endometriosis – refer to European Menopause and Andropause Society (EMAS) position statement on managing the menopause in women with a past history of endometriosis for further information. Refer a patient if symptomatic with persistent pain.	Take advice from menopause specialist about HRT and then refer to gynaecologist for further investigations	Include gynaecology discharge summary within the referral letter if referring to the menopause specialist
Family history suggestive of a moderate to high risk of breast cancer	Refer to family history clinic before referring to menopause specialist	Try alternatives to HRT. Refer to NICE guideline CG164 familial breast cancer for when to refer to family history clinic
Oestrogen dependent cancers such as breast cancer/BRCA gene	Refer to breast cancer specialist and the menopause specialist	Try alternatives to HRT
Hormone dependent cancers, gynaecological cancers: including endometrial cancer/ovarian cancer	Refer to menopause specialist	Include correspondence from gynae-oncologist within the referral letter
Patients with hormone dependent cancers including endometrial cancer and ovarian cancer	Refer to menopause specialist	Include correspondence from gynae-oncologist
Testosterone replacement therapy in menopausal women with low sex desire	Refer to menopause specialist for advice	Perform baseline serum total testosterone include result within the referral letter.

18. Links to useful resources and websites for clinicians and patients

18.1 Links to useful resources

- Women's Health Concern, Understanding the risk of breast cancer, www.womens-health-concern.org
- NICE NG23, Menopause: diagnosis and management, https://www.nice.org.uk/guidance/ng23
- Women's Health Concern, factsheet on 'migraine and HRT' useful in managing perimenopausal women with migraine, https://www.womens-health-concern.org/wp-content/uploads/2020/12/18-WHC-FACTSHEET-Migraine-and-HRT-DEC2020.pdf
- HRT preparations and equivalent alternatives (Updates on availability are posted on the BMS MIMS website)
- BMS, Bioidentical HRT, https://thebms.org.uk/publications/consensus-statements/bioidentical-hrt
- Royal College of Obstetricians & Gynaecologists (RCOG) *information leaflet* on alternative treatments to manage menopausal symptoms, https://www.rcog.org.uk/for-the-public/menopause-and-later-life/hrt-and-alternatives/
- *FSRH Clinical Guideline. Contraception over age 40 Guideline https://www.fsrh.org/standards-and-guidance/documents/fsrh- guidance-contraception-for-women-aged-over-40-years-2017/*

18.2 Links to useful websites

- www.menopausematters.co.uk
- www.womens-health-concern.org
- www.imsociety.org, https://www.imsociety.org/education/impart-registration/(IMPART module free online training)
- www.pcwhf.co.uk
- www.emas-online.org
- www.daisynetwork.co.uk
- www.nos.org.uk
- http://www.shef.ac.uk/FRAX/
- http://www.menopause.org/
- www.mhra.gov.uk
- www.fsrh.org
- www.rcog.org.uk

19. HRT shortages and their management

For further information around HRT drugs shortages management, please see:

- NHS England Specialist Pharmacy Service website
- British Menopause Society resource on HRT supply

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