SEL Gynaecology Network: Primary Care Guidelines

14.02.24 (revised 07.04.25)

Due for review date: 07.04.27



Introduction

Primary care guidelines to support the diagnosis and management of menopause including women who have premature ovarian insufficiency.

This guide has been produced utilising published guidance and in collaboration with clinical and non-clinical staff across the South East London (SEL) Gynaecology Network, South East London Integrated Care Board, South East London Primary Care representatives, South East London Cancer Alliance, South East London Integrated Medicines Optimisation Committee (IMOC), and with input from Gynaecology colleagues where relevant.

All prescribing should be in line with the <u>SEL Joint Medicines Formulary</u>.

It is intended to be a guide to assist Primary care colleagues in decision making and does not replace clinical judgement.

We encourage users of this document to seek advice from primary or secondary care colleagues when they are unsure, the later using established communication channels (e.g. Consultant Connect and e-RS Advice and Guidance).

Shortages of medicines are becoming a frequent issue that hinders patients getting access to their medicines in a timely manner. Please note, when medicines used in the management of menopause are subject to shortages, clinicians may recommend an alternative which is not on the SEL JMF. Please see the medicines supply tool, which can be accessed from the SPS website (linked here). The tool provides up to date information on medication shortages, and also includes advice on the prescribing of alternative products. Once supply resolves, patients should be transferred back to their original formulary option, following discussion with patients that original formulary option is appropriate.

Please note that information on the HRT preparations and topical testosterone preparations included in the Joint Medicines Formulary for SEL can be found at:

- Oral and transdermal HRT
- Vaginal HRT Preparations
- <u>Topical Testosterone Preparations</u> (off-label use in low libido)

Authors and Governance

Version	Date signed off	Date of next review
1	14.02.24	14.02.26
2	07.04.25	07.04.27

These guidelines have been drawn up with input from a number of clinicians across South East London. Key authors include Dr Ritu Agarwal (SEL Primary Care Lead for Gynaecology) and a number of clinical specialists across SEL, including Sadhna Murphy (Associate Director Medicines Optimisation), Deborah Bruce (Consultant Gynaecologist), Laura Salter (Consultant Gynaecologist) and Haitham Hamoda (Consultant Gynaecologist).

The guidelines were reviewed and signed off in subspeciality workstream meetings and by the subspeciality clinical lead.

Medicines and prescribing recommendations made within these guidelines have been reviewed and approved by the SEL Integrated Medicines Optimisation Committee (IMOC).

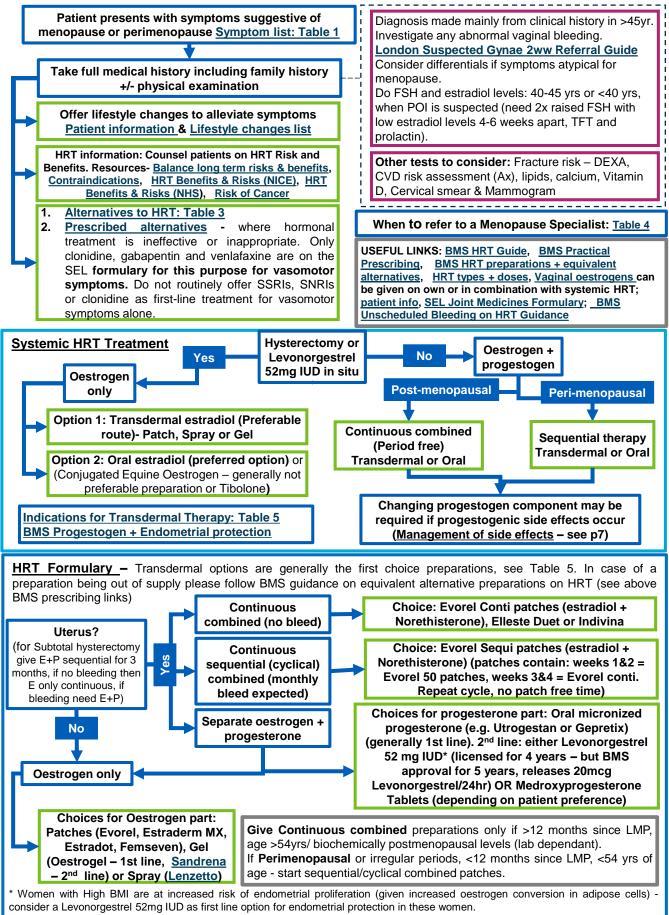
Guidelines have also been circulated to LMC representatives, Planned Care Leads in each borough, SEL Cancer Alliance, SEL GP Cancer Leads and all SEL GP's via the bulletin for review and comment.



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1 Menopause Guidelines

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	Collaborative HRT for specific clinical conditions
Preparations for atrophic vaginitis and other genitourinary syndrome of menopause: 1. Vaginal lubricants 2. Vaginal moisturisers: water based & oil based. 3. Vaginal oestrogens: creams, pessaries or ring (not suitable for women on aromatase inhibitors).	HRT + previous Endometrial ablation: Combined HRT regimen (either sequential or continuous regimen) should be used to reduce the risk of endometrial hyperplasia in any residual endometrial tissue.
 Wohen on alonatase inhibitors). Other medication which can be initiated by specialist team: DHEA pessary (Prasterone) - <u>SEL IMOC Formulary</u> recommendation. Ospemifene (AMBER 2) - <u>SEL IMOC</u> Formulary recommendation Use vaginal oestrogens with caution in women with history of hormonal dependent cancer, liaison with specialist recommended to ensure not contraindicated in patient. <u>Vaginal oestrogens</u> can be- Prescribed with or without systemic oestrogen Used long term (no known increased cancer or VTE risks) 	 HRT + Premature Ovarian Insufficiency: Where there is a loss of ovarian activity under the age of 40 years either spontaneously or iatrogenic: Offer HRT or combined hormonal contraceptive to patient, unless contraindicated. Continue HRT until natural age of menopause (average 51 years). Reassess need for ongoing therapy after that. Assess fragility risk (DEXA scan/FRAX scoring).
 Prescribed without progesterone - minimal systemic absorption Inserted (pessary) or applied topically to vulva Prescribe daily for first two weeks, reduce gradually to maintenance of twice weekly. Maximum benefit usually around 1-3 months. Approximately 1 year supply of topical vaginal therapy is equivalent to one tablet of oral HRT. If using condoms or diaphragm for contraception – advise to use 	HRT + Endometriosis: Hysterectomy for endometriosis may need progestogens despite removal of uterus to avoid reactivation of microdeposits of endometriosis elsewhere which can cause pain. This needs discussion regarding risks of oestrogen only (reactivation of microdeposits of endometriosis elsewhere causing pain) vs risk of adding in progestogen (increases risk of breast cancer). Seek advice from menopause specialist if unsure. <u>BMS article</u>
 tablet or vaginal ring as creams can damage condoms and diaphragms. <u>HRT & Contraception: Table 6</u> <u>Preparations (choice dependent on patient preference)-</u> Estradiol 10mcg vaginal Tablets. Ovestin®Cream-(Estriol 1000mcg/g)-500mcg/0.5g applicator dose Blissel® Gel- (50mcg/g) 50 mcg/ 1g applicator dose 	HRT + Migraine: Migraine with aura is not a contraindication for HRT but use non-oral body identical oestrogen like gel or patch at the lowest possible dose. Levonorgestrel 52mg IUD preferable option for progestogens as less hormone fluctuation. Effective management of vasomotor symptoms is a recognised way of improving migraines. <u>BMS article</u>
 Imvaggis®Pessaries-(Estriol 30mcg) 30mcg per pessary dose Estring® Vaginal ring- (Estradiol 2mg) 7.5mcg/24 hours- Replace every 3 months Intrarosa® (Prasterone) DHEA Pessary 6.5mg daily and only to be used after failure of vaginal oestrogen on specialist advice. 	HRT + Breast Cancer: In women with a history of breast cancer offer non-hormonal alternative therapies first. Refer to menopause specialist if poor symptom control <u>BMS article</u> , <u>Risks & Benefits of HRT with</u> <u>Breast Cancer</u>
Testosterone replacement: Transdermal therapy may be useful for women with low sexual of	drive when maximum effective dose of HRT has not helped

Transdermal therapy may be useful for women with low sexual drive when maximum effective dose of HRT has with low libido symptoms. In SEL this medication has been approved for formulary use as AMBER 1 now. If clinically appropriate, please use A&G (baseline testosterone levels need to be done prior to advice and guidance). However, this can be initiated by a GP with an extended role in gynaecology.

There are many issues affecting libido, ensure to rule out other causes that affect libido.

Testosterone implants and patches have now been withdrawn. Testosterone gels are now commonly used in women who require androgen replacement due to the lack of available alternatives. In UK, these products are licensed only for use in men and their use in women is an out of licence use for the product. The preparations currently available are: Option 1 - Tostran (In SEL this is 1st line) 2-3 measures a week (each application contains 10 mg testosterone). (SEL IMOC formulary recommendation 105, acknowledging that this may change during shortages) Option 2 - Testogel (40.5 mg/2.5mg) one sachet used over 8 days.

Monitoring: (advise patient not to have a blood test shortly after using testosterone gel)

-Total testosterone (and FAI) at baseline to ensure baseline levels not above the normal reference range.

-Re-assess 2-3 months after starting: to ensure levels remain within reference range. Continue if improvement in symptoms. It can take 4-6 months to evaluate the full adherence, efficacy and tolerability of the treatment.

-Yearly review in primary care to ensure risk/benefit and to check total testosterone (and FAI) and side effects (unwanted hair growth, frontal baldness, deepening of voice).

Testosterone replacement in menopause, BMS Testosterone explained, BMS statement on testosterone Testosterone for women factsheet, BMS Update on HRT Supplier Availability, Topical testosterone risk of harm to children following accidental exposure, Topical Testosterone Preparations JMF link,

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Management of side effects

Suspected problem	Advice
Compliance	Allow 3-6 months on treatment for full effect & counsel on importance of compliance.
Oestrogen dose	Review correct application before increasing dose. Increase dose or change administration route if the patients has an incomplete symptom response. Blood test to check oestrogen levels may also be considered.
Poor patch adhesion / skin irritation	Ensure that patient is rotating application site. Switch to alternative brand or oestrogen gel for poor patch adhesion.
Incorrect diagnosis	Review indications (e.g. thyroid disease)/ refer
Poor absorption	Consider change to route of administration
Unmanaged expectations	Counsel patient on bleed patterns, treatment adherence and regular review, weight gain, HRT is not a contraceptive, etc.
Drug interactions	Enzyme inducers (e g phenytoin) may lower the circulating hormone levels - consider changing to non oral routes. Levonorgestrel 52 IUD is not affected.

Oestrogen-related side effects (may occur continuously or randomly throughout cycle)

Side effects	Management
Breast tenderness or enlargement	 Wearing a well fitted bra or sports bra; Topical or oral Non-steroidal anti- inflammatory if not contra-indicated- can be purchased OTC; Can be alleviated by a low-fat, high carbohydrate diet Reduce the dose of oestrogen
Nausea, bloating, or dyspepsia	 May be helped by adjusting timing of oestrogen dose or taking with food Change the route of administration to a non-enteral formulation.
Headaches or migraines	 Can be triggered by fluctuating oestrogen levels – try switching to a transdermal route as this produces more stable oestrogen levels.
Angioedema	 Oestrogens can cause or exacerbate angioedema symptoms. Especially for patients with hereditary angioedema. Consider menopause expert referral.

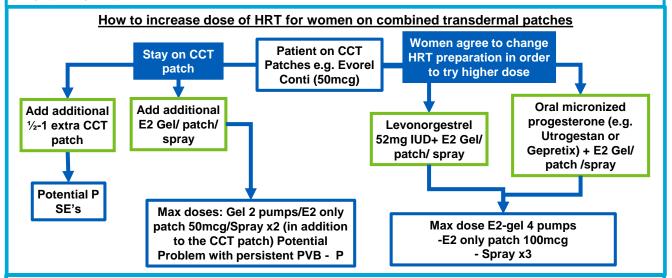
Progestogenic side effects (may occur in cyclical pattern during cyclical HRT's progestogen phase)

Side effects	Management
Fluid retention Breast tenderness Lower abdominal pain Back pain Headaches or migraines Mood swings Depression Acne	 Type: Change progestogen type (e.g. from more androgenic norethisterone to Oral micronized progesterone (e.g. Utrogestan or Gepretix) Route: Change route of progestogen delivery (e.g. from oral to transdermal, vaginal, or Levonorgestrel 52mg IUD). May benefit women experiencing nausea/bloating or dyspepsia with oral preparations. 100mg vaginal progesterone tablets or 200mg vaginal pessaries (utrogestan) or oral micronized progesterone can be used off-license vaginally in same dosage regimen. Regimen: Reduce the duration of progestogen regimen. Progestogens can be taken for 10-14 days/month in sequential regimen, so swapping from 14 to 10 days product may have benefit. Product: changing to a product with lower dose of progestogen Frequency: reduce progestogen dosing frequency by either switching to a long-term regimen of administering progestogen for 14 days every 3 months (only suitable for women without natural regular periods, risk of insufficient endometrial protection needs discussing fully with patient and possible specialist input) or continuous progestogen- provides better long-term protection than cyclical. Changing to continuous combined therapy often reduces progestogenic side effects with established use. Only suitable for postmenopausal women.

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When to stop HRT: Stop HRT when risks outweigh benefits and patient agrees to stop. Consider gradual withdrawal of HRT to limit a recurrence of symptoms (depend on clinical judgement, pending investigation). Consider stopping HRT temporarily if the following occur:

Sudden breathlessness or cough with blood-stained sputum; • Hepatitis, jaundice, or liver enlargement; • Sudden severe chest pain (even if not radiating to left arm) or unexplained swelling/severe pain in calf of one leg; • BP above systolic 160mmHg or diastolic 95mmHg; • New contraindication to treatment e.g. a recent diagnosis of hormone dependent cancer; • Serious neurological effects, including unusually severe, prolonged headache, especially: If it is the first time, or getting progressively worse, There is sudden partial or complete loss of vision, Sudden disturbance of hearing or other perceptual disorders, Dysphasia, Vasovagal episode or collapse, First unexplained epileptic seizure, Weakness, motor disturbances, or very marked numbness suddenly affecting one side/part of body; • Prolonged immobility after surgery or leg injury – if on oral HRT- switch to transdermal preparation. <u>NICE CKS Guidance</u>



If there is suboptimal management of symptoms (oestrogen), problems with bleeding (progestogens). Consider increasing the dose of the progestogen if patient is on high dose HRT (100mcg) as per <u>BMS Guidance (after</u> discussion around risks and benefits of higher progestogen dose)

Prescribed estrogen dose for ultra-low, low standard, moderate and high dose regimens (BMS)

	Ultra-low dose	Low Dose	Standard dose	Moderate dose	High dose
Oestrogel	½ pump	1 pump	2 pumps	3 pumps	4 pumps
Sandrena	0.25 mg	0.5 mg	1 mg	1.5-2 mg	3 mg [*]
Lenzetto spray	1 spray	2 sprays	3 sprays	4-5 sprays [*]	6 sprays [*]
Patch	12.5 µg	25 µg	50 µg	75 µg	100 µg
Oral estradiol	0.5 mg	1 mg	2 mg	3 mg^	4 mg^

* Off-license use mg = milligrams Off-license use – rarely required to achieve symptom control

Progestogen dose per licensed estrogen dose in the baseline population (BMS)

Estrogen dos	e Micronised	Progesterone	Medroxy pr	ogesterone	Norethis	sterone	LNG-IUD
	continuous	sequential	continuous	sequential	continuous	sequential	(52mg)
Ultra/Low	100 mg	200 mg	2.5 mg	10 mg	5 mg*	5 mg [*]	
Standard	100 mg	200 mg	2.5-5 mg	10 mg	5 mg*	5 mg*	One – for up to 5
Moderate	100 mg	200 mg	5 mg	10 mg	5 mg	5 mg	years of use
High	200 mg	300 mg	10 mg^	20 mg^	5 mg	5 mg	

* 1 mg provides endometrial protection for ultra-low to standard dose estrogen but the lowest stand-alone dose currently available in the UK is

5 mg (off-license use of three noriday POP i.e 1.05 mg, could be considered if 5 mg is not tolerated).

^ There is limited evidence in relation to optimal MPA dose with high dose estrogen; the advised dose is based on studies reporting 10 mg

providing protection with up to moderate dose estrogen.

The table has been drawn up as a practical guide based on a combination of pharmacokinetics, clinical trials and clinical experience. The dose equivalents are subject to significant individual variations in absorption and metabolism.

s μg = micrograms

Unscheduled Bleeding on HRT

 Common in the first 3 months and will usually settle. Counsel whappen in the first few months of HRT initiation during first com Exclude 2ww criteria (refer to local guidelines). For a signific not need 2 week wait referral. Patient can continue using the Hence Pan-London Suspected Gynaecology Cancer Referral Guide If continues beyond 3 months consider alteration of progestoge Rule out other causes-Check smear history, Vaginal examinat Detailed history-Type of HRT sequential or continuous combin extent of bleeding, Compliance with medication. Continued bleeding after 6 months – BMS Guidance (p6) flow assess endometrium with scan +/- refer for endometrial sample Consider further adjusting the progestogen at this stage. Seek The BMS have released guidance to support with the mana assessment and management should follow this guideline Link for SEL Primary Care educational module on 'Managing U unscheduled bleeding on hormone replacement therapy 	nsultation to manage expectations. cant majority of patients bleeding on HRT does HRT. de en dose or type (see below section). tion, STI screen, Exclude local vaginal causes. hed, Is she on the correct type, Severity and wchart on unscheduled bleeding on HRT - ing or hysteroscopy, exclude 2WW criteria. & A&G if appropriate. aggement of unscheduled bleeding on HRT, e - link
 <u>HRT Continuous combined</u> Increase dose of progestogen Consider adding 100mg PO micronized progesterone to regime If using micronized progesterone increase to 200mg daily (off license), if using Medroxyprogesterone acetate increase from 5-10mg PO daily* Change the progestogen component to an alternative oral preparation or to a Levonorgestrel 52mcg IUD* Change to a preparation with a different progestogen component Add Desogestrel 75mcg PO to regime* Change to a sequential preparation for a further 12 months 	 increase to 20mg po 12-14/7 per cycle* Increase duration of cyclical progestogen to 14 or 21/7 of a 28/7 HRT cyclical preparation
 * Please note this dose regime is an unlicensed dose, but in line <u>Progestogens in HRT regimes and doses</u> Medroxyprogesterone acetate 10mg for 14 days per cycle, 5m formulary as medroxyprogesterone – do not prescribe as Prov Oral micronized progesterone (e.g. Utrogestan or Gepr 200mg for 14 days per cycle for sequential Norethisterone 5mg PO for 14 days per cycle (*dose different to combined Levonorgestrel 52mg IUD - has a license for 4 years for endor 	ng daily- continuous combined (In SEL vera as not on SEL JMF) r etix) 100mg daily for continuous combined or to BNF), 0.5-1mg PO daily for continuous

be used for 5 years.

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Table 1: Symptoms of the menopause (women may experience 1 or more symptoms) MENQOL Questionnaire – to measure menopause symptoms

Vasomotor	Psychological	Urinary/ vaginal	Others
Hot Flushes	Nervousness/ anxiety/	Vaginal infections	Skin
Night sweats	panic attacks	Painful sex	itching/
Sweating	Anger/irritability	Post coital	crawling
Shivering	Confusion	bleeding	sensation
Increased	Depression	Irritation/ itching	Change in
pulse	Forgetfulness	Decreased libido	bleeding
Feeling faint	Difficulty concentrating	Dysuria	pattern
Weakness	Energy fatigue/loss	Atrophic vagina	Joint pains
Vertigo	Low Self-Esteem	Urinary frequency	Weight
Nausea	Memory deterioration	Urinary urgency	gain
Insomnia	Psychosexual	Post micturition	Headaches
Palpitations	dysfunction	bleeding	Tiredness
	Decreased libido	Urge/ stress	
	Poor sleep	incontinence	
	Tearfulness		

Table 2: Lifestyle recommendations to alleviate symptoms

Symptom	Lifestyle Modification
Hot flushes + night sweats	Regular exercise, healthy BMI, wearing lighter clothing, sleeping in a cooler room with silk pillows, using a fan, reducing stress & avoiding possible triggers (e.g. smoking, caffeine, spicy foods, alcohols)
Sleep disturbances	Avoiding exercise late in the day, maintain regular bedtime, mindfulness and sleep apps. NHS recommended wellbeing apps (<u>headspace</u> , <u>calm</u> , <u>Sleepio</u> .)
Mood + anxiety disturbances	Adequate sleep, regular physical activity and relaxation exercises, mindfulness
Cognitive symptoms	Exercise and good sleep hygiene Self Care

Table 3 – Prescribable alternatives to HRT – bms advice

Can be helpful in women who do not want to/cannot take hormonal medication. However, there is limited research available for these products and the research that does exist is related to short term symptoms. None of these can be prescribed (BOUGHT OTC), can be expensive and generally have no impact on CVD or osteoporosis prevention or managing vaginal issues: • Black cohosh can improve vasomotor menopausal symptoms but can have side effects such as liver toxicity and interactions with tamoxifen- not recommended for women with history of hormone dependent cancers; • Phytooestrogens like soy and red clover contain plant like oestrogen that may be beneficial in reducing short-term symptoms; . Acupuncture - women should be advised that no scientific evidence exists that this works any better than a placebo, but that all placebos work to some degree or other. They should be advised to find a registered practitioner; . CBT for hot flushes and night sweats- patient advice

Table 5: Indication for transdermal HRT

Preferred route in most patients as it avoids first pass metabolism and have no impact on the clotting cascade and can be especially useful if there are other risk factors. It should be the only route to be considered in these patients- *Individual preference, *Poor symptom control with oral HRT, *GI disorders affecting oral absorption, *Previous or family history of VTE, *BMI>30, *Variable blood pressure control, *Migraine, *Current use of hepatic inducing enzyme medication, *Gall bladder or liver disease

Table 4: When to refer to Menopause Specialist or seek
A&G

- Complex medical history (e.g endometriosis)
- Carriers of faulty genes such as BRCA1/2 or Lynch, known to increase risk of cancer - <u>CanRisk</u>
- Current, past or suspected hormone dependent cancers.
- Ineffectiveness or persistent side effects despite following treatment pathway.
- Recurrent bleeding which has been fully investigated, no abnormality detected but not resolved.
- Low libido not improving on maximum effective dose of oestrogen – specialist advice for considering testosterone therapy.
- Women with suspected POI -baseline tests required prior to referral for POI: Pelvic ultrasound, DEXA, FSH/LH and estradiol levels x2 (raised FSH>30, estradiol <92) done 4-6 weeks apart, TFT + prolactin.

Table 6: HRT and Contraception

A woman is potentially considered to be fertile for 2 years after her last menstrual period if <50 years of age, and for 1 year if >50 years of age. In patients requiring contraception and free of all contraindications consider offering the following HRT/contraceptive options: *Oestrogen only pill, patch or gel and Levonorgestrel 52mg IUD (other IUDs are not licensed for endometrial protection) • Combined hormonal contraception (if eligible but only up until age 50) • Sequential combined HRT (pill or patch) and progestogenonly contraception (tablet, implant, injection) • If hormonal contraception is declined: advise barrier methods with sequential combined HRT.

When to stop contraception: • >50 years - 1 year after LMP; • < 50 years- 2 years after LMP; • 45- 55 years -Levonorgestrel 52mg IUD inserted after 45 years can stay in till age 55 for contraception but only for 5years if used as part of HRT also (unlicensed use for 5years for HRT); • Stop hormonal contraception at 55 years of age; • Do not check FSH or estradiol if on HRT / combined hormonal contraception; • If >50 years with amenorrhea due to progestogen only method- check FSH: if FSH level >30 IU/L stop after 1 year.

Table 7: HRT Counselling + Review

-Ensure patient understands HRT's risks + benefits & importance of progesterone uterine protection where applicable.

-Setting realistic expectation on what HRT can achieve. -Emphasise need for contraception where applicable.

-Explain about bleed patterns in women with uterusunscheduled bleeding is a common side effect within first 3 months but should be reported at first review at 3-4m or promptly if occurs after that. Use of CCT will not stop periods in menstruation women.

-Review patients after 3-4m after HRT initiation or change and at least annually thereafter.

- At review assess symptom control, tolerability, and compliance; reassess risks relating to HRT and choice and dose of HRT (consider dose reduction as patients gets older, switching to transdermal preparation where appropriate to reduce VTE risks); check blood pressure; emphasise importance of keeping up to date with national breast and cervical screening programme; emphasise on regular breast examination, bone health optimisation and NHS health checks.

- HRT can be continued for as long as the benefits 10 outweigh the risks

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Abbreviations

	Collaborative	<u> </u>
Abbreviation	Definition	
2WW	2 Week Wait Pathway	
A&G	Advice and Guidance	
Ax	Assessment	
BMI	Body Mass Indicator	
BMS	British Menopause Society	
BRCA 1	Breast Cancer gene 1	
BRCA 2	Breast Cancer gene 2	
BSO	Bilateral Salpingo-Oophorectomy.	
CBT	Cognitive Behaviour Therapy	
ССТ	Continuous Combined Therapy	
CVD	Cardiovascular disease	
DEXA	Dual energy x-ray absorptiometry	
DHEA	Dehydroepiandrosterone sulphate	
E2 Gel	Estradiol Gel	
E + P	Oestrogen and Progestogen	
FAI	Free Androgen Index	
FRAX	Fracture Risk Assessment Tool	
FSH	Follicle-stimulating hormone	
GI Disorder	Gastrointestinal Disorder	
GSM	Genitourinary Syndrome of Menopause	
HRT	Hormone Replacement Therapy	
IUS/IUD	Intrauterine System/Device	
JMF	Joint Medicines Formulary	
LH	Luteinizing Hormone	
LMP	Last Menstrual Period	
MENQOL	Menopause-specific Quality of Life	
OTC	Over the Counter	
P + SEs	Progesterone and Side Effects	
POI	Premature Ovarian Insufficiency	
SPS	Specialist Pharmacy Service	
SNRIs	Serotonin and norepinephrine reuptake inhibitors	
SSRIs	Selective serotonin reuptake inhibitors	
ТАН	Total Abdominal Hysterectomy	
TFT	Thyroid Function Test	
VTE	Venous Thromboembolism	