Menopause and HRT[1] guidance

NHS Rotherham Clinical Commissioning Group

CLINICAL DIAGNOSIS		
<40 years	**40-45 years**	**≥45 years**
▪ Symptoms ▪ No/infrequent periods for >3 months ▪ Not on COCP[2]/high dose progesterone ▪ Test: 2x FSH[3] 4-6 weeks apart. If FSH>30 diagnosis of PREMATURE OVARIAN INSUFFICIENCY – choice of treatment with HRT or COCP	▪ Symptoms ▪ Menstrual cycle changes ▪ Not on COCP[2]/high dose progesterone ▪ Test - consider only if need for definitive diagnosis: 2x FSH 4-6 weeks apart. If FSH>30 diagnosis of menopause	▪ Symptoms ▪ No period for >12 months NO role for FSH testing
▪ Or due to surgical removal of uterus and ovaries		

MENOPAUSAL SYMPTOMS and treatment options	
VASOMOTOR (HOT FLUSHES, NIGHT SWEATS)	➢ HRT - 1st line ➢ Do not offer SSRI[4]/SNRI[5] or clonidine (limited efficacy and side effects) ➢ Alternative self-care with isoflavones or black cohosh (consider content/safety)
PSYCHOLOGICAL (LOW MOOD)	➢ HRT – 1st line ➢ CBT[6] ➢ Do not offer SSRI[4]/SNRI[5] to patients with no diagnosis of depression ➢ Rule out hypothyroidism or depression
LOSS OF LIBIDO	➢ HRT ➢ Refer to gynae for topical testosterone supplementation if HRT alone ineffective (under Shared Care Protocol arrangements)
UROGENITAL ATROPHY	➢ Vaginal oestrogen – as stand-alone treatment OR could be used in addition to HRT (if systemic hormones not contra indicated)
VAGINAL DRYNESS	➢ Moisturisers and lubricants – used alone or in addition to vaginal oestrogen or systemic HRT NOT SUITABLE FOR PRESCRIBING ON NHS – patients should be advised self-care
HRT also beneficial for bone mineral density/ osteoporosis, reduces risk of fragility fracture	

PATIENT ASSESSMENT PRIOR TO INITIATION
- Symptoms - Menstrual and gynaecological history, including contraception - Other medical history, including family history - Risk factors and C/I[7] to systemic HRT - Check BP, height, weight, and BMI - For women under age of 40 on diagnosis of early menopause assess bone mass density and repeat in 2-3 years - Some HRT preparations incur double NHS prescription charge (see product list) – consider if relevant

GENERAL CONTRAINDICATIONS TO SYSTEMIC HRT – refer to specialist
• history of breast cancer or oestrogen-dependent tumour • untreated endometrial hyperplasia • undiagnosed vaginal bleeding • arterial thromboembolic disease • current/ recurrent VTE[8] • thrombophillic disorder • liver disease (with abnormal LFTs[9])

HRT CHOICE - consider: uterus, last bleeding, and need for contraception

Hysterectomy or Mirena in situ?

NO → **COMBINED HRT**

YES → **OESTROGEN ONLY HRT**

LAST BLEEDING?

in last 12 months → **CYCLICAL/ SEQUENTIAL combined HRT**

After 1 year consider swapping

none in last 12 months (NB. POP/LNG-IUS no VB) → **CONTINUOUS combined HRT**

TRANSDERMAL 1st line:
Sequential combined patch e.g. Evorel Sequi, FemSeven Sequi

OR

Oestrogen only patch/gel/pill combined with:

- **IUS**[10] (**Mirena** – licensed for 4 years for HRT use but may remain in situ for up to 5 years for HRT)
- **Micronized progesterone** (Utrogestan) 200mg ON[11] for 12 days of cycle (day 15-26 of a 28-day cycle)
- **Medroxyprogesterone acetate** (Provera) 10mg OD[12] for 12 days

ORAL 2nd line:
Sequential combined pill e.g. Femoston

TRANSDERMAL 1st line:
Continuous combined patch e.g. Evorel Conti, FemSeven Conti

OR

Oestrogen only patch/gel/pill combined with:

- **IUS** (**Mirena** – licensed for 4 years for HRT use but may remain in situ for up to 5 years for HRT)
- **Micronized progesterone** (Utrogestan) 100mg ON every day (unlicensed but with good evidence base)
- **Medroxyprogesterone acetate** (Provera) 5mg OD every day

ORAL 2nd line:
Continuous combined pill e.g. Femoston Conti

gonadomimetic e.g. Tibolone

TRANSDERMAL 1st line:
Patch e.g. Evorel 50
Gel e.g. Oestrogel, Sandrena
Spray e.g. Lenzetto

ORAL 2nd line:
Tablet e.g. Elleste solo

gonadomimetic e.g. Tibolone

VAGINAL SYMPTOMS/ UROGENITAL ATROPHY

YES → VAGINAL ± systemic HRT

Vaginal oestrogen – systemic absorption is minimal and progestogen opposition is not required, may be continued long term

ESTRIOL based:

- **1st line cream:** Ovestin (0.1%) N.B. 0.01% is not cost effective
- Pessary: Imvagiss 30mcg
- Gel: Blissel 50mcg/g

ESTRADIOL based:

- **2nd line pessary:** Vagifem 10mcg
- Ring: Estring 7.5mcg/24hrs (change 3 monthly, max treatment duration 2 years)

Vaginal moisturisers:
AS SELF-CARE ONLY – not to be initiated/ prescribed on NHS (Replens, Sylk, Yes)

CONTRACEPTION NEEDED?

Perimenopause / under 50 years	Menopause / over 50 years
for 2 years after last period	for 1 year after last period
All progestogen only contraception methods are safe to use alongside sequential HRT	

CONTRACEPTION

- HRT is not a contraceptive (only Mirena is licensed as HRT and hormonal contraception)
- Contraception required for 2 year after last menstrual period for women <50 years and for 1 year for women >50 years
- Progestogen only hormonal contraception (i.e. POP[13], implant, Mirena/Levosert, Kyleena, Jaydess) - no vaginal bleeding

OESTROGEN COMPARATIVE DOSES

Given comparison is approximate and not directly equivalent

Dose equivalency for conjugated equine oestrogen to estradiol is unclear

ORAL	PATCH	Sandrena gel	Oestrogel pump	Lenzetto spray
1mg estradiol	~ 25mcg	~ 0.5g	~ 1 pump actuations	~ 1 spray actuation
2mg estradiol	~ 50 mcg	~ 1 g	~ 2 pump actuations	~ 2 spray actuations
3-4mg estradiol	~ 75-100 mcg	~ 1.5 g (max licensed)	~ 4 pump actuations (max licensed)	~ 3 spray actuations (max licensed)

Highlighted above are the usual starting dose for each corresponding formulation

PROGESTOGEN CHOICE FOR COMBINED HRT

Use dydrogesterone or micronized progesterone as 1st choice of progestogen (non-androgenic) due to favourable risk profile (lower risk of breast cancer, VTE[8] and CVD[14])

Class		Examples	Route	Comments
Testosterone analogues	ANDROGENIC	**Norethisterone**	transdermal oral	▪ good cycle control ▪ unfavourable effect on lipids ▪ systemic absorption of levonorgestrel from Mirena is minimal ▪ Mirena – is the only IUS[10] which may be used as part of HRT[1]
		Levonorgestrel	intrauterine transdermal oral	
Progesterone analogues		**Medroxyprogesterone acetate (Provera)**	oral	▪ unfavourable effect on lipids
	NON-ANDROGENIC	**Dydrogesterone**	oral	▪ favourable risk profile (reduced risk of breast cancer, VTE[8] and CVD[14]) ▪ only available in combined HRT[1] oral preparations
Bioidentical		**Micronised progesterone (Utrogestan)**	oral	▪ less progestogenic side-effects ▪ favourable risk profile (reduced risk of breast cancer, VTE[8] and CVD[14]) ▪ no effect on lipids ▪ less effective bleeding control ▪ may cause sedation – to be taken at night

GONADOMIMETICS i.e. Tibolone 2.5mg OD[12]

- synthetic steroid with oestrogenic, progestogenic and androgenic activity
- continuous combined HRT[1] with no bleeding, indicated for post-menopausal women
- conserves bone mass and helps with vasomotor, psychological and libido symptoms
- not recommended as 1st line option due to unfavourable risk profile, similar to combined HRT[1] - increased cancer and VTE[8]

HRT[1] PRODUCT OVERVIEW						
Type		**Formulation**	**Brand**	**Oestrogen content**	**Progestogen content**	**Comments**
Cyclical/ sequential combined (intact uterus)	1st line	Patches	Evorel Sequi	Estradiol 50 micrograms	Norethisterone 170micrograms	Peri- and post-menopausal women; monthly bleed, double Rx charge
		Patches	FemSeven Sequi	Estradiol 50 micrograms	Levonorgestrel 10micrograms	
	2nd line	Tablets	Femoston	Estradiol 1mg, 2mg	Dydrogesterone 10mg	Postmenopausal women at least 6 months since last period; monthly bleed, double Rx charge
	3rd line	Tablets	Elleste Duet	Estradiol 1mg, 2mg	Norethisterone 1mg	Peri- and post-menopausal women; monthly bleed, double Rx charge
		Tablets	Clinorette	Estradiol 2mg, 2mg	Norethisterone 1mg	
		Tablets	Cyclo-progynova	Estradiol val. 2mg	Norgestrel 500microgram	
		Tablets	Tridestra	Estradiol val. 2mg	Medroxyprogesterone 20mg	Peri- and post-menopausal women; quarterly bleed, double Rx charge
		Tablets	Trisequens	Estradiol 2mg, 2mg, 1mg	Norethisterone 1mg	Postmenopausal women at least 6 months since last period, monthly bleed, double Rx charge
		Tablets	Novofem	Estradiol 1mg	Norethisterone 1mg	
Continuous combined (intact uterus)	1st line	Patches	Evorel Conti	Estradiol 50microgram	Norethisterone 170microgram	Post-menopausal women at least 18 months since last period; no bleed
		Patches	FemSeven Conti	Estradiol 50microgram	Levonorgestrel 7micrograms	Post-menopausal women at least one year since last period; no bleed
	2nd line	Tablets	Femoston Conti	Estradiol 500microgram, 1mg	Dydrogesterone 2.5mg, 5mg	Post-menopausal women at least one year since last period; no bleed
	3rd line	Tablets	Elleste Duet Conti	Estradiol 2mg	Norethisterone 1mg	
		Tablets	Kliofem	Estradiol 2mg	Norethisterone 1mg	
		Tablets	Kliovance	Estradiol 1mg	Norethisterone 500microgram	
	4th line	Tablets	Indivina	Estradiol val. 1mg, 2mg	Medroxyprogesterone 2.5mg, 5mg	Post-menopausal women at least three years since last period; no bleed
		Tablets	Premique Low Dose	Conj. oestr 300micrograms	Medroxyprogesterone 1.5mg	Post-menopausal women at least one year since last period; no bleed

Unopposed oestrogen (if uterus is intact an adjunctive progestogen must be used)	1st line	Patches	Evorel	Estradiol 25, 50, 75, 100microgram		Peri- and post-menopausal women
		Patches	Estradot	Estradiol 25, 37.5, 50, 75, 100microgram		Post-menopausal women at least one year since last period. Smallest patches.
		Patches	Estraderm MX	Estradiol 25, 50, 75, 100microgram		Post-menopausal women at least one year since last period
		Patches	Progynova TS	Estradiol 50, 100microgram		Postmenopausal women more than one year postmenopause
		Gel	Oestrogel	Estradiol 0.06%		Post-menopausal women at least one year since last period
		Gel	Sandrena	Estradiol 500microgram, 1mg		
		Transdermal spray	Lenzetto	Estradiol 1.53mg per metered dose		Post-menopausal women at least 6 months after last menses or surgical menopause
	2nd line	Tablets	Elleste Solo	Estradiol 1mg, 2mg		Peri- and post-menopausal women
		Tablets	Zumenon	Estradiol 1mg, 2mg		Postmenopausal women at least 6 months since last period
		Tablets	Bedol	Estradiol 2mg		Peri- and post-menopausal women
		Tablets	Progynova	Estradiol val. 1mg, 2mg		
		Tablets	Premarin	Conj. oestr 300microgram, 625microgram, 1.25mg		Post-menopausal women at least one year since last period
Adjunctive progestogen	1st line	IUS	Mirena		Levonorgestrel 20mcg/24hrs	Protection from endometrial hyperplasia during oestrogen replacement therapy. Should be removed after 4 years as per license for HRT, may remain in situ for 5 years (license for contraception)
		Oral capsules	Utrogestan		Progesterone 100mg, 200mg	For adjunctive use with oestrogen in post-menopausal women with an intact uterus, continuous regimen is unlicensed (but with good evidence base)
	2nd line	Tablets	Provera or Climanor		Medroxyprogesterone 5mg, 10mg	For adjunctive use with oestrogen in peri- and post-menopausal women

Local/ vaginal oestrogen	1st line	Vaginal cream	Ovestin	Estriol 0.1%		Atrophic vaginitis; cost effective estriol vaginal cream (CCG preferred brand)
	2nd line	Vaginal tabs	Vagifem	Estradiol 10micrograms pessaries		Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women
	3rd line	Vaginal tabs	Vagirux	Estradiol 10micrograms pessaries		
		Vaginal tabs	Imvaggis	Estriol 30microgram pessaries		Local treatment of vaginal symptoms of oestrogen deficiency in postmenopausal women
		Vaginal ring	Estring	Estradiol 7.5micrograms		One ring inserted and worn continuously for 3 months. Replace with new ring at 3-month intervals. Max continuous treatment period 2 years
		Vaginal gel	Blissel	Estriol 50micrograms/g		Local treatment of vaginal dryness in postmenopausal women with vaginal atrophy
		Vaginal cream	Generic preparation	Estriol 0.01%		Atrophic vaginitis and kraurosis in post-menopausal women. Pruritus vulvae and dyspareunia associated with atrophic vaginal epithelium, less cost effective option of vaginal estriol cream

FOLLOW UP/ REVIEW	
Commenced on HRT[1]	3 months after initiation
Established on HRT[1]	at least annually or ASAP[15] if vaginal bleeding occurs in patients with uterus
▪ At each review check blood pressure, height, weight and BMI[16] ▪ At each review discuss risk vs benefits and consider lowering dose or discontinuation ▪ Reassess and document regularly, as risk of adverse effects changes over time	
In women with premature menopause systemic HRT[1] is recommended (if not contra indicated) until the average age of menopause (51 years) to prevent early onset of osteoporosis, CVD[14], Alzheimer's disease, Parkinson Disease and cognitive decline.	

VAGINAL BLEEDING PROBLEMS	
In women with uterus unscheduled vaginal bleeding is a common side effect of HRT[1] within the first 3 months of treatment and the clinical management is dependent on the type of HRT[1]	
Patient on CYCLICAL HRT[1] - consider causes i.e. compliance, interactions, malabsorption, pathology	
Heavy/ prolonged withdrawal bleeding	Increase/change progestogen OR reduce oestrogen
Early bleeding in progestogen phase	Increase/change progestogen
Painful bleeding	Change type of progestogen
Spotting before withdrawal period	Increase oestrogen dose
Irregular bleeding	Change HRT[1] regime OR increase progestogen
Persistent heavy/ prolonged/ breakthrough or painful bleeding	Refer to gynaecology for investigation
CONTINUOUS COMBINED HRT[1]	
Spotting/ recurrent bleeding	Increase/change progestogen, convert to cyclical if other options fail
Heavy or continuing after 6 months of start/ change of HRT[1]	Refer to gynaecology for investigation
New bleeding after 12 months of amenorrhea	Refer to gynaecology for investigation

HRT[1] SIDE EFFECTS			
OESTROGENIC		**PROGESTOGENIC**	
Nausea/ heartburn	Wait – s/e[17] generally settle within 3 months If not, or severe, lower dose or change the route	PMS[18] type symptoms	Change progestogen type/ route/ regimen (i.e. to continuous combined HRT[1])
Breast tenderness		Mood changes	
Nipple sensitivity		Acne/ greasy skin	
Bloating		Breast tenderness	
Headaches		Bloating	
Leg cramps		Headaches	

STOPPING HRT[1]
Duration of HRT[1] need to be individualised – there is no max duration of therapy
• Could be gradually reduced to limit recurrence of symptoms in short term OR • Could be immediately stopped but symptoms may recur short term only
No difference to symptom control long term

RISKS ASSOCIATED WITH HRT[1] USE

Summary of HRT risks during current use and current use plus post-treatment from age of menopause up to age 69 years, per 1000 women with 5 years or 10 years use of HRT

	Risks over 5 years use (with no use or 5 years current HRT use)		**Total risks up to age 69** (after no use or after 5 years HRT use†)		**Risks over 10 years** (with no use or 10 years current HRT use)		**Total risks up to age 69** (after no use or after 10 years HRT use†)	
	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**
Risks associated with **combined oestrogen-progestogen HRT**								
Breast cancer	13	**+8**	63	**+17**	27	**+20**	63	**+34**
Sequential HRT	13	**+7**	63	**+14**	27	**+17**	63	**+29**
Continuous combined HRT	13	**+10**	63	**+20**	27	**+25**	63	**+40**
Endometrial cancer	2	-	10	-	4	-	10	-
Ovarian cancer	2	**+ <1**	10	**+ <1**	4	**+1**	10	**+1**
Venous thromboembolism (VTE)§	5	**+7**	26	**+7**	8	**+13**	26	**+13**
Stroke	4	**+1**	26	**+1**	8	**+2**	26	**+2**
Coronary heart disease (CHD)	14	-	88	-	28	-	88	-
Fracture of femur	1.5	-	12	-	1	-	12	-
Risks associated with o**estrogen-only HRT**								
Breast cancer	13	**+3**	63	**+5**	27	**+7**	63	**+11**
Endometrial cancer	2	**+4**	10	**+4**	4	**+32**	10	**+32**
Ovarian cancer	2	**+ <1**	10	**+ <1**	4	**+1**	10	**+1**
Venous thromboembolism (VTE)	5	**+2**	26	**+2**	10	**+3**	26	**+3**
Stroke	4	**+1**	26	**+1**	8	**+2**	26	**+2**
Coronary heart disease (CHD)	14	-	88	-	28	-	88	-
Fracture of femur	0.5	-	12	-	1	-	12	-

†Best estimates based on relative risks of HRT use from age 50. For breast cancer this includes cases diagnosed during current HRT use and diagnosed after HRT use until age 69 years; for other risks, this assumes no residual effects after stopping HRT use.

RISK OF BREAST CANCER – KEY POINTS:

- The increased risk is linked to systemic HRT (all types), but not vaginal oestrogen to treat local symptoms
- The risk is higher for combined oestrogen-progestogen HRT than oestrogen-only HRT
- The risk is higher with continuous HRT (daily progestogen) than with sequential HRT
- The risk is increased during use of HRT, reduces after stopping but remains increased for >10 years after stopping HRT compared with women who have never used HRT
- Risk increases further with duration of HRT use
- No/little increased risk with use of HRT for less than 1 year (including past users)
- The risk is unaffected by the type of oestrogen or progestogen, or the route of administration (oral or transdermal)

RISK OF ENDOMETRIAL CANCER – KEY POINTS:

- The increased risk is linked to oestrogen-only HRT and increases with longer duration
- No increased risk with combined HRT

RISK OF OVARIAN CANCER – KEY POINTS:

- Evidence suggesting there may be increased risk with all systemic HRT which falls after cessation
- Not discussed by NICE

RISK OF CARDIOVASCULAR DISEASE – KEY POINTS:

- If HRT initiated under the age of 60 there is no increased risk of CVD
- HRT is not contra-indicated in pre-existing CVD risk factors if they are optimally managed
- The risk of stroke with oral (but not transdermal) oestrogen is slightly increased but is very low in all women under the age of 60

RISK OF VENOUS THROMBOEMBOLISM – KEY POINTS:

- Transdermal HRT preparations are 1st choice option – same risk as baseline population
- The increased risk is associated with oral HRT (combined and oestrogen-only), particularly in the first year of use but not observed with transdermal preparations
- The risk is higher with combined oestrogen-progestogen HRT than with oestrogen-only preparations
- Risk increases further with longer duration of HRT use
- Risk increases further with dose of oestrogen
- Conjugated equine oestrogen has higher risk of VTE than estradiol
- The highest risk is with conjugated equine oestrogen and medroxyprogesterone acetate combination (i.e. Premique)
- Oral estradiol with dydrogesterone is not associated with increased risk (i.e Femoston)
- The risk returns to baseline (no history of HRT use) on cessation

RISK OF DIABETES – KEY POINTS:

- HRT (oral and transdermal) is not linked with increased risk of developing type 2 diabetes
- Blood glucose control should not be adversely affected in women with type 2 diabetes using HRT

GLOSSARY OF ABBREVIATIONS:

1. **HRT** – hormone replacement therapy
2. **COCP** – combined oral contraceptive pill
3. **FSH** - follicle-stimulating hormone
4. **SSRI** – selective serotonin reuptake inhibitor
5. **SNRI** – serotonin–norepinephrine reuptake inhibitor
6. **CBT** - cognitive behavioural therapy
7. **C/I** – contra-indication
8. **VTE** - venous thromboembolism
9. **LFT** – liver function test
10. **IUS** – intra uterine system i.e. hormone releasing coil
11. **ON** – at night
12. **OD** – daily
13. **POP** - progestogen-only pill
14. **CVD** - cardiovascular disease
15. **ASAP** – as soon as possible
16. **BMI** - body mass index
17. **s/e** – side effects
18. **PMS** - premenstrual syndrome