Menopause and HRT

From NICE Menopause CKS/NG23 (2015), Joint position statement on menopause management BMS/RCOG (Post Reproductive Health, 2022;0(0)1), BMS guidelines (2020) and BNF (2021)

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Symptoms (due to falling oestrogen levels)

- Hot flushes, night sweats.
- Menstrual irregularities.
- Sleep disturbance.
- Vaginal dryness.
- Urinary problems.
- Joint and muscle pains.
- Loss of libido.
- Mood changes.
- Cognitive disturbance.

Diagnosis and investigations

Diagnosis is made from a clinical history of typical symptoms in a woman ≥45y, but remember:

- Investigate any abnormal bleeding first.
- Consider differentials if symptoms atypical (e.g. alcohol, drugs, thyroid, anxiety, tumours).

Arrange FSH if:

- <45y: 2 results >30 IU/L 4–8w apart is suggestive of early menopause, or premature if <40y.
- >50y and amenorrhoeic and wants to stop hormonal contraception: if 1 result >30 IU/L, she can stop contraception in 12m (FSRH consensus is that she is likely to no longer be fertile by then).

Treatment options

Lifestyle

- Regular exercise.
- Healthy diet and BMI.
- Stop smoking.
- Reduce alcohol.
- Avoid symptom triggers, e.g. spicy food.
- Reduce stress.
- Relaxation exercises.
- Sleep hygiene.

Hormone replacement therapy (HRT)

- First line for:
  - Vasomotor symptoms.
  - Low mood.
- Beneficial for:
  - Sexual function.
  - Urogenital atrophy.
  - Musculoskeletal symptoms.
  - Bone mineral density.

Alternatives to HRT

- CBT for low mood and anxiety.
- Isoflavones (soy) and black cohosh may help flushes but preparations vary in content/safety.
- Evidence supports the use of SSRIs and SNRIs in women who can't have/don't want HRT. Counsel regarding side-effects.

Contraindications to HRT: refer to menopause specialist!

- History of breast cancer or oestrogen-dependent tumour.
- Untreated endometrial hyperplasia.
- Undiagnosed vaginal bleeding.
- Uncontrolled hypertension.
- Arterial thromboembolic disease.
- Current or recurrent VTE (unless anticoagulated).
- Thrombophillic disorder.
- Liver disease (with abnormal LFTs).

Note: migraine is not a contraindication to HRT but use transdermal.

Counselling about HRT risks *(note contraindications above)*

Condition	Risk
Breast cancer	• Lifestyle factors (obesity, excess alcohol) may have greater impact on breast cancer risk than HRT. • Small increased risk: risk greater with combined HRT than oestrogen-only. • HRT is *unlikely* to increase risk of breast cancer in women <50y, and risk of exposure from HRT should be counted from aged 50y – which is average age of natural menopause. • Micronised progesterone and dydrogesterone may be safest progestogens.
VTE	• HRT increases VTE risk, but individual risk depends on other risk factors, and risk generally low in early post-menopause years. • Oral preparations carry higher risk. Transdermal oestrogen appears safer as it avoids first-pass liver metabolism and doesn't activate clotting factors (yet to be confirmed by RCTs). • Micronised progesterone appears to be the safest progestogen but more data is needed.
Cardiovascular disease (CVD)	• CVD is the commonest cause of death in postmenopausal women. • HRT does not increase the risk of cardiovascular disease in women <65y. • HRT may be cardioprotective in younger postmenopausal women (<10y from LMP), but evidence not strong enough to recommend as primary prevention of CVD.
Stroke (CVA)	• Oral HRT increases the risk of stroke; transdermal preparations appear safer (observational evidence). • Risk of CVA depends on other cardiovascular risk factors but is generally low in this age group.
Ovarian cancer	• Slight increased risk (suggested from epidemiological studies, although causation cannot be inferred).

Menopause and HRT: which HRT?

From NICE Menopause CKS/NG23 (2015), British Menopause Society guidelines (2020) and BNF (2021)

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Types of HRT

Oestrogen-only HRT
For women *who have had a TOTAL hysterectomy* or those *with an IUS.*
Unopposed oestrogens cause endometrial proliferation: women with a uterus MUST have progestogen to stop this.

Sequential combined HRT
For *peri-menopausal women*
(some endogenous hormone production will lead to irregular bleeding on a continuous regime).
Daily oestrogen with *sequential* progestogen (usually in last 12–14d of pack/month) to trigger a bleed.

Continuous combined HRT
For *postmenopausal women* (>12m since LMP).

Contains *daily* oestrogen and progestogen.

Swap from sequential combined to continuous combined: after >1y of sequential HRT or age >54y.

Which HRT?

Does she have a uterus?

Yes → **Does she require contraception?**
(<55y and sexually active and menstruating)
Contraception NOT required if:
- *≤50y and has been amenorrhoeic for ≥2y.*
- *>50y and has been amenorrhoeic for ≥1y.*

No → **Has she been amenorrhoeic for >1y?**

Yes → **Offer continuous combined HRT:**
- Continuous combined pill.
- Continuous combined patch.
- Oestrogen-only pill, patch, gel or spray with:
  - 52mg IUS.
  - 5mg medroxyprogesterone acetate daily.
  - 100mg micronised progesterone daily.

No → **Offer sequential combined HRT:**
- Sequential combined pill.
- Sequential combined patch.
- Oestrogen-only pill, patch, gel or spray with:
  - 52mg IUS.
  - 10mg medroxyprogesterone acetate 14d/cycle.
  - 200mg micronised progesterone 12d/cycle.

Yes → **Offer any of the following HRT/contraception options:**
- Oestrogen-only pill, patch, gel or spray + 52mg IUS.
- Combined hormonal contraception (if eligible).
- Sequential combined HRT (pill or patch) + progestogen-only contraception (tablet, implant, injection).
- If amenorrhoeic with progestogenic contraception: could use continuous combined HRT instead of sequential.
- If declines hormonal contraception: advise barrier methods with sequential combined HRT.
- **Stop hormonal contraception at age 55y.**

No → **Offer oestrogen-only HRT**
- Pill, transdermal patch, gel or spray.

UNLESS she has had:
- Sub-total hysterectomy.
- A hysterectomy due to moderate/severe endometriosis.

These women should be started on combined HRT.

Reviews
(3m after starting and then annually)

- Discuss symptom control, side-effects and ongoing indication.
- Check BP, BMI and screening up to date.
- Reinforce lifestyle optimisation.

Stop HRT when…
- Risks outweigh benefits – no arbitrary limits should be placed on age or duration of use.
- Patient happy to stop.

Troubleshooting

- **Persistent/abnormal bleeding beyond 6m: investigate**.
- **Bleeding after starting continuous combined HRT**: if doesn't settle after 3–6m, swap to sequential HRT for another 12m.
- **Heavy bleeding on sequential HRT***:* increase dose/duration of progestogen.
- **Progestogenic side-effects:** switch to alternative progestogen or consider IUS.

HRT: formulations (from MIMS 2022)

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Oral: usually cheapest. **Transdermal:** lower VTE/CVA risk so use preferentially if >60y, overweight or migraines. **If urogenital symptoms predominate:** consider using vaginal oestrogens instead.

Sequential combined

Route	Oestrogen	Progestogen	Name	Cost (28d)
Oral	Oestradiol 1–2mg	Dydrogesterone 10mg (14 tabs)	Femoston	£5.39
	Oestradiol valerate 2mg (70 tabs)	Medroxyprogesterone acetate 20mg (14 tabs) + 7d placebo	Tridestra (long-cycle preparation)	£6.83
	Oestradiol valerate 2mg	Norethisterone 1mg (12 tabs)	Clinorette	£3.08
	Oestradiol 1mg		Novofem	£3.81
	Oestradiol 1–2mg		Elleste Duet	£3.07
	Oestradiol 1mg (10 tabs) 2mg (12 tabs)	Norethisterone 1mg (10 tabs)	Trisequens (phasic preparation)	£3.70
Patch	Oestradiol 50mcg/24h	Norethisterone 170mcg per 24h (2 patches/w for 14d)	Evorel Sequi	£11.09
	Oestradiol 50mcg/24h	Levonorgestrel 10mcg per 24h (1 patch/w for 14d)	FemSeven Sequi	£13.18

Continuous combined

Route	Oestrogen	Progestogen	Name	Cost (28d)
Oral	Conjugated equine oestrogen 300mcg	Medroxyprogesterone acetate 1.5mg	Premique Low Dose	£2.17
	Oestradiol 0.5–1mg	Dydrogesterone 2.5–5.0mg	Femoston Conti	£8.14
	Oestradiol 1–2mg	Medroxyprogesterone acetate 2.5–5.0mg	Indivina	£6.86
	Oestradiol 1mg	Norethisterone 0.5mg	Kliovance	£4.40
	Oestradiol 2mg	Norethisterone 1mg	Elleste Duet Conti	£5.67
			Kliofem	£3.81
	Oestradiol 1mg	Progesterone 100mg	Bijuve	£8.14
Patch	Oestradiol 50mcg/24h	Norethisterone 170mcg per 24h (2 patches/w)	Evorel Conti	£13.00
	Oestradiol 50mcg/24h	Levonorgestrel 7mcg per 24h (1 patch/w)	Femseven Conti	£15.48

Oestrogen-only (only if no uterus/Mirena in place)

Route	Oestrogen	Name	Cost (28d)
Oral	Conjugated equine oestrogen 300mcg/625mcg/1.25mg	Premarin	£2.02/£1.34/£1.19
	Oestradiol 2mg	Bedol	£1.69
	Oestradiol 1–2mg	Elleste Solo	£1.69
		Progynova	£2.43
		Zumenon	£2.30
Patch	Oestradiol 40/80mcg per 24h	Elleste Solo MX	£5.19/£5.99
	Oestradiol 25/50/75/100mcg per 24h	Estraderm MX	£5.50/£5.51/£6.42/£6.66
		Evorel	£3.42/£3.88/£4.12/£4.28
	Oestradiol 25/37.5/50/75/100mcg per 24h	Estradot	£5.99/£6.00/£6.02/£7.00/£7.27
	Oestradiol 50/75/100mcg per 24h	Femseven	£6.04/£6.98/£7.28
	Oestradiol 50/100mcg per 24h	Progynova TS	£6.30/£6.90
Gel	Oestradiol gel (0.06%) 2–4 pumps (1.5–3.0mg) per 24h	Oestragel 80g pump	Approx. £4.20–£8.40
	Oestradiol gel (0.1%) 0.5–1.5mg per 24h	Sandrena 0.5/1.0mg sachets	Approx. £5.08–£5.85
Spray	Oestradiol 1.53mg/metred dose 1–3 sprays per 24h	Lenzetto 8.1ml (56 actuations)	Approx. £3.45–£6.90

Progestogen/progesterone-only (to be used with oestrogen-only HRT if has uterus)

Route	Progestogen	Dose	Name	Cost (28d)
Oral	Medroxyprogesterone acetate	10mg daily for 14d/cycle (sequential) or 5mg continuously (continuous combined)	Climanor	5mg = £3.27
Oral/vaginal	Micronised progesterone (can be used vaginally: off-licence)	200mg for 10–12d/cycle (sequential) or 100mg continuously (continuous combined)	Utrogestan	100mg = £4.28 200mg = £4.10
Intrauterine	Levonorgestrel 52mcg	20mcg/24h	Mirena, Levosert or Benilexa	Approx £1.00

Other HRT preparations

Route	Content	Dose	Name	Cost (28d)
Oral	Tibolone (gonadomimetic)	2.5mg	Livial	£10.36 (generic £4.76)