Section 2: Endometrial cancer risk factors in women taking HRT

The incidence of endometrial cancer in relation to a woman's individual risk factors and specific HRT preparation are outlined in this section. Table 1 summarises this evidence and categorises these risk factors into major or minor, to enable triage of women who present with unscheduled bleeding onto the correct assessment pathway (non-urgent, urgent and urgent suspicion of cancer pathway (USCP)) as outlined in Sections 3 and 4.

Tables 2 and 3 (combined in Appendix 1) outline prescribed estrogen dosages, in relation to specific transdermal and oral preparations, and the recommended progestogen dose, for ultra-low to high dose estrogen.

Table 1: Major and minor factors affecting risk of endometrial cancer in women taking HRT

Major risk factors	• BMI ≥ 40 • Genetic predisposition to endometrial cancer (Lynch / Cowden syndrome) • Estrogen-only HRT for more than 6 months in women with a uterus • Tricycling HRT (quarterly progestogen course) for more than 12 months • Prolonged sHRT regimen: use for more than 5 years when started in women aged ≥ 45 • 12 months or more of using norethisterone or medroxyprogesterone acetate for < 10 days / month or, micronised progesterone for < 12 days / month, as part of a sequential regimen
Minor risk factors	• BMI 30-39 • Unopposed estrogen for more than 3 months but less than 6 months • Tricycling HRT (quarterly progestogen course) for more than 6 months but less than 12 months • More than 6 months, but less than 12 months, of using norethisterone or medroxyprogesterone acetate for < 10 days / month or, micronised progesterone for < 12 days / month, as part of a sequential regimen • Where the progestogen dose is not in proportion to the estrogen dose for > 12 months (including expired 52 mg LNG-IUD)* • Anovulatory cycles, such as in PCOS • Diabetes

* There is limited evidence relating to the impact on endometrial cancer risk; this should be a research priority to enable improved stratification of risk/pathways (see Table 3).

Endometrial cancer risk factors independent of HRT use

- **Risk factors for endometrial hyperplasia, independent of HRT, should be identified. Major risk factors include BMI ≥ 40 and hereditary conditions such as Lynch or Cowden syndrome. Minor risk factors include BMI 30-39, diabetes and polycystic ovarian syndrome. Optimisation of modifiable factors can, in themselves, reduce episodes of unscheduled bleeding on HRT and endometrial cancer risk.**

Endometrial cancer is the fourth most common cancer in the UK; the reported incidence in women who present with postmenopausal bleeding (PMB), i.e. those who are not taking HRT, is 3-10%.[10, 11] The incidence increases with age; rates (per 100,000 women) rise sharply from the age of 55 and reach a peak at age 70 to 74. The age-related incidence in the UK is 0.7% for women aged 50-54, 1.2% aged 55-59, 1.3% aged 60-64, and 1.5% aged 65-74.[12]

Genetic factors can increase risk by 30-50%, with conditions such as Lynch and Cowden syndrome considered major factors.[13] Obesity is the strongest risk factor for endometrial cancer with 40% of cases associated with this; BMI ≥ 40 confers a tenfold higher risk when compared to a BMI within the normal range.[14] Consideration of weight loss strategies, and support for this, is associated with a reduction in endometrial hyperplasia and cancer risk.[15, 16] Other factors that affect the bioavailability of estrogen and insulin-like growth factor-1 (IGF-1), such as diabetes, PCOS and unstable liver disease, can increase endometrial cancer risk.[11]

Risk of endometrial cancer in HRT users who DO NOT report unscheduled bleeding

Effect of HRT preparation on endometrial cancer risk

- **Inform amenorrhoeic postmenopausal women taking a continuous combined preparation (ccHRT), which contains standard dose estrogen and a proportionate progestogen dose, that endometrial cancer risk appears to be lower than in non-HRT users.**
- **Women taking a sequential preparation (sHRT) over the age of 45 should be offered, after five years of use or by age 54 (whichever comes first), a change to ccHRT.**
- **In women using sHRT, offer a minimum of 10 days norethisterone (NET) or medroxyprogesterone acetate (MPA), or 12 days of micronised progesterone, per month; recommending two weeks per 28 day cycle with progestogen and two weeks without may help to reduce administration and prescribing errors.**
- **A monthly progestogen dose, in proportion to the estrogen dose, is recommended in women with a uterus. It should be noted that more than six months of unopposed estrogen or 12 months of tricycling (estrogen daily with a progestogen course every 3 months), are major risk factors for endometrial cancer.**
- **Counsel women there are limited data relating to the optimal progestogen dose needed to provide endometrial protection in women taking high dose estrogen (particularly in perimenopausal women taking sHRT).**

Continuous combined HRT (ccHRT):
Administration of daily (continuous) progestogen suppresses endometrial growth leading to amenorrhoea and atrophy.[17] This appears to reduce the risk of endometrial cancer, compared with non-users, with the greatest effect seen in women with a BMI ≥ 30.[18-20] In women who do not report unscheduled bleeding, the risk of endometrial cancer with ultra-low to standard dose estrogen, and a progestogen dose which is in proportion, is < 1%.[21] There are limited data assessing risk with moderate or high dose estradiol use. Table 2 outlines prescribed estrogen, in relation to specific transdermal and oral preparations for ultra-low, low, standard, moderate and high dosages.

Table 2: Prescribed estrogen dose for ultra-low, low, standard, moderate and high dose regimens

	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 ^ Off-license use – rarely required to achieve symptom control
mg = milligrams µg = micrograms

Sequential/cyclical HRT (sHRT):
In women over 50, who have no unscheduled bleeding and use medroxyprogesterone acetate (MPA) or norethisterone (NET) for 10-12 days of the month, the relative risk of endometrial cancer is similar to non-users. If these progestogens are used for less than 10 days, this risk is three-fold higher after six months use (RR 3.1, 95% CI 1.7-5.7).[21-23] Micronised progesterone (MP), in conjunction with standard dose estrogen, provides endometrial protection if given at a dose of 200mg for 12-14 days of the month for up to five years use.[24]

When compared to non-users, if sHRT (progestogen for 10-12 days) is used for more than five years, the risk of endometrial cancer is almost three times higher (RR 2.9 (95% CI 1.8-4.6)).[21-23] In women who are perimenopausal at the natural age (≥ age 45), switching to ccHRT should be offered after five years of sHRT or by age 54 (whichever comes first). It can also be considered after 12-18 months of sequential use, if women want to try ccHRT to see if they can achieve a bleed-free regimen at an earlier point.[25]

Tricycling (Long-cycle) Progestogen use and shortened progestogen regimens
This is where estrogen is given daily but a reduced progestogen course (7-10 days) is given every three months. When compared to use of a monthly progestogen course – NET or MPA for 10-12 days – the incidence of endometrial hyperplasia and cancer is higher; 7.5% vs 0% at 12 months (p=0.005) and 11% vs 1.4% by 36 months (p=0.01).[26, 27] The risk of endometrial cancer when tricycling incorporates moderate or high dose estrogen, or micronised progesterone, is unknown.

If a shortened duration of progestogen is considered in women with an intolerance to all progestogen types (including 52 mg LNG-IUD and off-license use of standard dose estrogen with 150 micrograms of daily desogestrel or x3 noriday tablets i.e. 1.05 mg NET), and in whom hysterectomy is not suitable or acceptable, informed counselling about endometrial risk, and the lack of evidence to support surveillance accuracy (six monthly ultrasound), should be discussed and documented.

Unopposed estrogen

There is strong evidence to support an increased risk of endometrial cancer with unopposed estrogen (i.e no progestogen use) in people with a uterus. A Cochrane review[27] reported high rates of endometrial hyperplasia, compared with placebo, after 12 and 24 months of standard dose unopposed estrogen use; OR 8.4 (95% CI 5.5-12.9) and OR 11.9 (95% CI 7.8-18.1) respectively. At one, two and three years, the proportion of women diagnosed with endometrial hyperplasia was 14.7%, 35.5% and 62% (respectively) – compared with 0.3% in the placebo group. There are limited data on risk with moderate or high dose unopposed estrogen use.

Progestogen type and endometrial protection

- **Counsel peri- and postmenopausal women considering use of a 52 mg LNG-IUD that it can be used for endometrial protection with ultra-low to high estrogen dosages for up to five years.**
- **Counsel women that a) tibolone and, b) progestogens (norethisterone, medroxyprogesterone acetate, levonorgestrel, dydrogesterone, micronised progesterone) when combined with standard dose estrogen, provide equivalent protection against endometrial cancer.**
- **Women taking moderate or high dose estrogen should be informed that the adequacy of endometrial protection provided by micronised progesterone is uncertain. The use of 200 mg as a continuous preparation, and 300 mg as a sequential preparation, should be offered if using high dose estrogen or if unscheduled bleeding occurs with ultra-low to moderate dose estrogen.**

Levonorgestrel 52 mg intra-uterine device (LNG-IUD)

Mirena® (52 mg LNG IUD) has a four-year license in the UK for progestogenic opposition of estrogen within HRT. The Food and Drug administration recommends use with a uterine depth less than or equal to 10 cm and NICE[28] advises against use if submucosal fibroids are more than 3 cm.

Studies have shown all 52 mg LNG IUD offer sufficient endometrial protection against ultra-low to high dose estrogen for up to five years of use in both peri- and postmenopausal women.[29-33] As a result, it is common and safe practice to use the 52 mg LNG IUD for five years within HRT regimens (outside manufacturer's license). There are a paucity of data relating to endometrial protection when estrogen above high dose is used and whether additional progestogen is required. Women should be counselled about this and the limitations of ultrasound in assessing the endometrium if unscheduled bleeding occurs (with the higher likelihood that hysteroscopy may be required). If at 4 years of use, new unscheduled bleeding develops, a change of 52 mg LNG IUD should be offered (if cancer exclusion tests are normal), particularly in women using over licensed estrogen dosages and in those with a BMI ≥ 40.

There are insufficient data to guide whether a malpositioned 52 mg LNG IUD provides adequate endometrial protection when used as part of HRT. Discuss with the woman a 52 mg LNG IUD may need to be correctly positioned at the fundus for maximum effectiveness. In relation to contraceptive use, the FSRH suggest '*as a general guide any of the following findings would usually be an indication to suggest that the IUC is removed and replaced: IUC > 2 cm from the fundus; IUC within the cervical canal (fully or partially); or IUC user experiencing symptoms that may be related to malpositioned IUC (e.g. pain or bleeding)*'.[29] One study[34] reported an association with irregular endometrial suppression and breakthrough bleeding when a specially designed intracervical LNG-IUD was compared to fundal placement; until high-quality studies assess efficacy for endometrial protection in HRT users, women who present with unscheduled bleeding and a malpositioned 52 mg LNG IUD should be offered alternate progestogens until IUD replacement.

Synthetic Progestogens

Synthetic progestogens such as NET, MPA, levonorgestrel and dydrogesterone, provide equivalent endometrial protection when the dose is in proportion to ultra-low, low, standard or moderate dose estrogen (see Table 3).[27, 35, 36] There are limited data assessing optimal dose for endometrial protection when high dose estrogen is prescribed.

Micronised progesterone (MP); dose and duration of use

MP can be used as an oral or vaginal (off-license) preparation. The Kronos Early Estrogen Prevention Study (KEEPs) and Postmenopausal Estrogen/Progestin Interventions trials (PEPI)[37, 38] compared sHRT (200 mg MP with standard dose estrogen) to placebo, over four years, and both reported equivalent endometrial cancer rates. The E3N cohort study[39] assessed endometrial cancer rates in 65,630 HRT users over ten years of whom 40% were taking oral MP; use for less than five years did not appear to increase risk (hazard ratio (HR) 1.39, 95% CI 0.99-1.97).

There is limited evidence assessing the long-term endometrial protective effect (> 5 years) when micronised progesterone is used as a continuous preparation and this should be considered a research priority. Although the European Prospective Investigation into Cancer and Nutrition (EPIC) study reported a two-fold association between micronised progesterone use and endometrial cancer, when compared with non-users (HR 2.42, 95% CI 1.53–3.83), the majority of participants used sequential, rather than continuous preparations, and duration of HRT was not adjusted for.[35]

There are insufficient data to advise on endometrial cancer risk when micronised progesterone, at a dose used for low or standard dose estrogen, is used in combination with moderate or high dose estrogen. Until evidence relating to safety with moderate and high dose estrogen is available, a pragmatic approach needs to be considered, as the risk to breast tissue from increasing the progesterone dose is also unknown; the use of 200 mg as a continuous preparation and 300 mg as a sequential preparation should be offered if using high dose estrogen[24, 39-42] or, if unscheduled bleeding occurs with low to moderate dose estrogen (Table 3). This should be considered a research priority as high-quality outcomes may enable lower dosage use in women taking high-dose estrogen or, conversely, may stratify if women with risk factors for endometrial cancer (diabetes, raised BMI) should be offered increased dose micronised progesterone with lower estrogen dosages.