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Progestogens and endometrial protection

Key points:

- Unopposed estrogen replacement is associated with a significant increase in the risk of endometrial hyperplasia that is both dose and duration dependent with exposure between one and three years.
- Non-hysterectomised women require progestogen administered for 12–14 days in a sequential regimen and daily in a continuous combined regimen to minimise the risk of endometrial hyperplasia and endometrial cancer associated with unopposed estrogen exposure.
- Long-term use of sequential combined HRT for >5 years may be associated with a small increase in risk of endometrial hyperplasia and endometrial cancer, with the risk being dose and duration dependent in relation to progestogen intake.
- Studies suggest that women taking sequential HRT with less than 10 days of progestogen each month are at increased risk of endometrial hyperplasia and endometrial cancer.
- However, progestogen intake in the recommended doses for 12-14 days a month does not appear to be associated with a significant increase in risk of endometrial hyperplasia for up to 5 years of use.
- Systematic review evidence showed oral micronised progesterone provides endometrial protection if applied sequentially for 12–14 days/month in a dose of 200 mg/day for up to 5 years.
- The dose of the progestogen should be proportionate to the dose of estrogen. Women who require high dose estrogen intake should consider having their progestogen dose increased to ensure adequate endometrial protection.
- Based on current evidence, if progesterone was considered for vaginal administration (out of license use) in women who experience side effects with oral intake, this should be given in similar doses and durations to those applied to oral progesterone intake with HRT.
- Intrauterine progestogen administration through the 52 mg levonorgestrel releasing intrauterine device (IUD) provides adequate endometrial protection for up to 5 years. The Mirena IUD has a four-year license in the UK for progestogenic opposition of estrogen HRT. Studies have shown it to be effective and to offer sufficient endometrial protection for up to 5 years within HRT regimens.
- There are concerns related to the purity, potency and safety of compounded progesterone products used within compounded bioidentical HRT products. There is a lack of evidence to suggest that the dosage of progesterone used in compounded preparations provides sufficient endometrial protection. The use of compounded products is not recommended. In addition, many such compounded products deliver progesterone transdermally in cream or gel preparations. The absorption of the latter is variable with fluctuating tissue availability and as a result may not provide sufficient endometrial protection.

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- For the majority of women with unscheduled bleeding on HRT, modifying progestogen intake often controls the bleeding, especially in women who experience unscheduled bleeding in the first few months after commencing HRT.
- Women who continue to have unscheduled bleeding beyond 4-6 months despite modifying their progestogen intake or where there is a concern about the clinical presentation or bleeding amount/ pattern should be assessed to exclude endometrial pathology.

Introduction

Progestogen administration is required to oppose naturally produced or administered estrogens to provide endometrial protection. Within HRT regimens, this should be delivered for at least the same duration as that produced during the luteal phase of the monthly cycle and in the recommended doses to protect against the risk of endometrial hyperplasia and endometrial cancer.[1-3]

This includes progestogens administered for 12–14 days a month in sequential regimens and continuous daily intake in continuous combined HRT regimens. Studies have shown that shorter durations and lower doses of progestogen intake are likely to be associated with an increased risk of breakthrough bleeding, endometrial hyperplasia and endometrial cancer.

For the majority of women with unscheduled bleeding on HRT, modifying progestogen intake would often control the bleeding especially in women who experience unscheduled bleeding in the first few months after commencing HRT. However, women who continue to have unscheduled bleeding beyond 4-6 months despite modifying their progestogen intake or where there is a concern about the clinical presentation or bleeding amount/pattern should be assessed to exclude endometrial pathology.[4]

Rationale for progestogen administration

The rationale for progestogen administration is to oppose and provide endometrial protection in all situations where estrogens are naturally produced or administered. A progestogen is required for at least the same duration as that produced during the luteal phase of the monthly cycle.

Non-hysterectomised women require progestogen administered for 12–14 days in sequential HRT regimens and daily in continuous combined HRT regimens to minimise the risk of endometrial hyperplasia and endometrial cancer associated with unopposed estrogen exposure.

Several studies in the 1970s reported an increased risk of endometrial hyperplasia and endometrial cancer with unopposed estrogen exposure.[5-10] These findings were subsequently confirmed in a large randomised controlled trial (RCT) in the 1990s, Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. PEPI included 596 postmenopausal women who were randomised in equal numbers to the following five groups: (1) placebo; (2) conjugated equine estrogen, 0.625 mg/day; (3) conjugated equine estrogen 0.625 mg/ day plus cyclic medroxyprogesterone acetate, 10 mg/day for 12 days a month; (4) conjugated

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equine estrogen, 0.625 mg/day plus continuous medroxyprogesterone acetate, 2.5 mg / day continuously; or (5) conjugated equine estrogen, 0.625 mg/day plus cyclic micronised progesterone, 200 mg/day for 12 days/month. Unopposed estrogen was associated with a substantially increased risk of endometrial hyperplasia compared with placebo [simple, complex or atypical hyperplasia RR 37.0; 95% CI 9.3-147.3]. The rate of endometrial hyperplasia with unopposed estrogen was 20% in the first year and 62% after 3 years.[1]

In addition, a Cochrane review showed that unopposed estrogen replacement is associated with a significant increase in the risk of endometrial hyperplasia that is both dose and duration dependent with exposure between one and three years.[11]

However, there was no significant difference in the risk of endometrial hyperplasia for any of the other groups that received progestogen compared with placebo. Micronised progesterone and medroxyprogesterone acetate were equivalent in providing endometrial protection.[11]

Progestogen intake is recommended with HRT in non-hysterectomised women in a sequential regimen in peri-menopausal women and continuous combined regimen regimens in postmenopausal women. Clinical evidence has demonstrated that continuous combined HRT provides more effective endometrial protection than sequential HRT.[2, 12-17]

Long-term use of sequential combined HRT for more than five years may be associated with a small increase in risk of endometrial hyperplasia and endometrial cancer, with the risk being dose and duration dependent in relation to progestogen intake. Studies have suggested that women taking sequential HRT regimens with less than 10 days of progestogen each month are at increased risk of endometrial hyperplasia and endometrial cancer.[2-3]

A systematic review by Stute et al. (2016) assessed the impact of micronised progesterone on the endometrium. Forty studies were included in the systematic review and it concluded that oral micronised progesterone provides endometrial protection if applied sequentially for 12–14 days/ month in a dose of 200 mg/day for up to five years.[18]

Based on current evidence, progestogen intake in non-hysterectomised women taking sequential HRT is recommended for 12–14 days a month. If the last menstrual period occurred less than one year (or less than two years in women with POI/early menopause) prior to starting HRT, a sequential combined regimen should be started (i.e. continuous estrogen with progestogen for 12–14 days per month).[2] This can be taken on days 15-26 of the cycle or for practicality it can be taken on days 1-12 of each calendar month.

After a minimum of one year of HRT, women who wish to avoid a monthly withdrawal bleed may attempt a switch to a continuous combined regimen which aims to give bleed-free HRT – this will also minimise the risk of endometrial hyperplasia. The timing of switching from sequential to continuous combined HRT should be considered in relation to the woman's age

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and the frequency of her menstrual cycles (prior to commencing HRT). Women under the age of 50 who had shorter durations of amenorrhoea before starting HRT are likely to need to continue a sequential intake for a longer duration before switching to continuous combined HRT intake.

Progestogen doses within HRT regimens

Based on Cochrane evidence, the suggested dose of progestogen given in a continuous combined HRT regimen would be a minimum of 0.5 mg/day of norethisterone or 2.5 mg/day of medroxyprogesterone acetate. For low-dose sequential regimens norethisterone a minimum of 1mg/day given for 10 days a month, oral micronised progesterone 200 mg/day for 12 days a month, medroxyprogesterone acetate 10 mg/day for 10–14 days a month or dydrogesterone 10 mg/day for 14 days a month would be suitable options.[11]

The dose of the progestogen should be proportionate to the dose of estrogen. While no data is currently available on the endometrial effects of high doses of estrogen and the optimal dose of oral or vaginal progestogen in this context, women who require high dose estrogen intake should consider having their progestogen dose increased to ensure adequate endometrial protection (e.g. micronised progesterone 300 mg for 12 days a month instead of 200 mg in cyclical HRT regimens or 200 mg daily on a continuous basis instead of 100 mg in continuous combined HRT regimens).

Studies have shown that continuous combined HRT is unlikely to increase the risk of endometrial cancer. The WHI estrogen and progestogen study reported a neutral effect on the risk of endometrial cancer with HRT compared to placebo during the intervention phase after five years of usage of HRT (HR 0.83; 95% CI 0.49–1.40). However, a significant reduction was noted with combined estrogen and progestogen intake compared to placebo in the post-intervention phase (HR 0.58; 95% CI 0.40–0.86) and with long term cumulative follow-up (HR 0.67; 95% CI 0.49– 0.91).[17]

Vaginal administration of progesterone within HRT regimens

Micronised progesterone can be also administered through the vaginal route although there is limited evidence assessing efficacy and the optimal regimen of vaginal progesterone administration in the context of HRT. In the UK, vaginal micronised progesterone preparations that offer the doses commonly used within HRT include 100 mg vaginal progesterone tablets (Lutigest) and 200 mg vaginal pessaries (Utrogestan or Cyclogest). The latter combinations are not licensed for use as HRT but can be used off license to provide the progestogen component of HRT in women who experience progestogenic side-effects with oral intake. In addition, in 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.

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In an RCT that included 100 women for a duration of 12 months, all women received transdermal estradiol in a dose of 50 micrograms patches and were randomised into four groups that assessed sequential intake of micronised progesterone from days 14-25 of a 28-day cycle. Two groups received oral micronised progesterone (in doses of 100 and 200 mg) and two groups received vaginal micronised progesterone (in similar doses of 100 and 200 mg). No significant differences were noted in endometrial thickness between the groups. However, the study did not assess endometrial histology and outcomes were assessed based on endometrial thickness assessed by transvaginal pelvic ultrasound.[19]

Stute et al. 2016 reported a systematic review on the impact of micronised progesterone on the endometrium. The authors suggested that estrogens with sequential micronised progesterone (4% corresponding to 45 mg/day for 10 days per month) or intermittent (100 mg every other day) for up to 3–5 years may be safe (off-label use). The authors acknowledged that there was lack of sufficient data regarding optimal vaginal administration within HRT to guide practice.[18]

However, more recently, a publication from the Early versus Late Intervention Trial with Estradiol (ELITE) showed that lower dose vaginal intake of progesterone resulted in a substantially higher rate of endometrial hyperplasia. This randomised double-blinded placebo-controlled trial, reported on the effect of oral estradiol plus vaginal progesterone against placebo on endometrial thickness, endometrial biopsy pathology, cervical cytology and total cancer incidence among healthy postmenopausal women.[20]

The study only included original ELITE participants with an intact uterus, who were randomised to either daily oral estradiol 1 mg/day with 4% vaginal micronised gel 45 mg/day for 10 days each month or placebo. Participants were assessed at baseline and annually during a median follow-up of 4.8 years.

Over up to 80 months of follow-up, participants randomised to oral estradiol plus vaginal progesterone had progressive and statistically significant increases in endometrial thickness ($p<0.001$), underwent more endometrial biopsies (RR 2.11; 95% CI 1.65-2.69) and had a substantially higher rate of endometrial hyperplasia on endometrial biopsy (RR 15.9; 95% CI 0.97-260.7) compared with the placebo group. The authors concluded that 10 days of vaginal progesterone 45 mg/day is insufficient to completely oppose the effect of oral estradiol 1 mg/day on the endometrium.[20]

More evidence in adequately powered studies is required to assess the optimal dose and duration of vaginal progesterone intake to provide optimal endometrial protection within HRT regimens.

Based on current evidence if progesterone was considered for vaginal administration (out of license use) in women who experience side effects with oral intake, this should ordinarily be given in similar doses and durations as suggested for oral progesterone intake with HRT.

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Transdermal administration of progestogens within HRT regimens

Transdermal synthetic progestogens

Norethisterone and levonorgestrel can be delivered transdermally in patches combined with estradiol (Norethisterone: Evorel Sequi [sequential] and Evorel Conti [continuous combined] / Estradot Conti 30 and Estradot Conti 40 [continuous combined]; Levonorgestrel: Femseven Conti [continuous combined]). Most patches use a matrix system in which the hormone is distributed evenly throughout the adhesive making it amenable to be cut in half if required (off license use).

Transdermal micronised progesterone

Micronised progesterone has variable transdermal absorption and is unlikely to provide sufficient estrogen opposition. A systematic review by Stute et al. (2016) concluded that transdermal micronised progesterone does not provide sufficient endometrial protection. Based on current evidence, micronised progesterone within HRT regimens should not be administered transdermally, as this is unlikely to provide sufficient endometrial protection.[18]

Further, most commercial preparations that deliver micronised progesterone transdermally include cream or gel preparations that are compounded products. In addition to the concerns about the varied absorption with this route of delivery, there are concerns related to the purity, potency and safety of compounded products. The latter is discussed in more detail in a separate section in this document.[2,25]

Intrauterine progestogen administration

Intrauterine progestogen administration through 52 mg levonorgestrel releasing intrauterine device (IUD) provides adequate endometrial protection in women receiving estrogen therapy. Only one product containing levonorgestrel 52 mg (the Mirena IUD) is licensed for progestogenic opposition of estrogen within HRT and has a four-year license in the UK. Studies have shown it to be effective and to offer sufficient endometrial protection up to five years within HRT regimens. As a result, it is common and safe practice to use the 52 mg levonorgestrel intrauterine device for five years within HRT regimens (out with its manufacturer's license). There is lack of evidence to guide practice regarding the efficacy of lower dose progestogen (e.g. 13.5 mg and 19.5 mg) releasing intrauterine devices. If lower dose progestogen releasing intrauterine devices are used as contraception in women receiving HRT, it would be recommended to add further progestogen (e.g. Utrogestan 100 mg daily or 200 mg for 12 days a month) to provide adequate endometrial protection.[21-24]

Progesterones within compounded bioidentical hormones – clinical safety concerns

Progesterones within compounded bioidentical hormone replacement therapies are manufactured as creams, lozenges and vaginal preparations by 'Specialist Pharmacies'. These do not follow the same regulatory pathways as conventional regulated HRT products and have not been scientifically evaluated in controlled randomised clinical trials for effectiveness and safety against placebo or conventional HRT. The use of such compounded products is not recommended.[2,25]

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There are concerns related to the purity, potency and safety of compounded products and there is a lack of evidence to suggest that the dosage of progesterone used in compounded preparations provides sufficient endometrial protection. In addition, many such compounded products deliver progesterone transdermally in cream or gel preparations. The absorption of the latter is variable with fluctuating tissue availability and as a result may not provide sufficient endometrial protection.[2,25]

HRT in women with subtotal hysterectomy

There is limited evidence to guide practice in relation to the role or need for progestogen replacement in women who have had subtotal hysterectomy. It is common practice to consider sequential progestogens for up to 3 months, and if no bleeding is noted with this, to consider it unlikely that residual endometrium is present and estrogen only HRT can be considered to be sufficient. Ongoing progestogen intake should be considered if there are concerns that the remnant cervical stump may contain residual endometrial tissue in women who experience cyclical bleeding with sequential HRT.[26]

HRT in women with endometriosis

Continuous combined HRT regimens should be considered in women following hysterectomy for severe endometriosis to prevent reactivation of residual disease and to potentially prevent malignant transformation of residual deposits. However, there is limited evidence available on this to guide clinical practice.[27,28]

HRT in women with endometrial ablation

Combined HRT regimens (sequential or continuous combined) should be used in women who have undergone endometrial ablation who wish to take HRT.[29]

Unscheduled bleeding on HRT

Women who continue to have unscheduled bleeding beyond 4-6 months despite modifying their progestogen intake or where there is a concern about the clinical presentation or bleeding amount/ pattern should have a transvaginal ultrasound scan assessment of the endometrial cavity and an endometrial biopsy where appropriate as per the recommendations of the BMS guideline on the management of unscheduled bleeding on HRT (https://thebms.org.uk/publications/bms-guidelines/management-of-unscheduled-bleeding-on-hormone-replacement-therapy-hrt/). Consideration should also be given to assessment of the endometrial cavity by hysteroscopy where clinically indicated or in cases with persistent bleeding and an endometrial biopsy obtained to assess for and exclude endometrial pathology.[2,30-32,35]

The risk of endometrial cancer in women with unscheduled bleeding on HRT is significantly lower than that with postmenopausal bleeding in women not on HRT especially in women who had not been experiencing bleeding before commencing HRT.[4]

For the majority of women with unscheduled bleeding on HRT, modifying progestogen intake often controls the bleeding especially in women who experience unscheduled bleeding in the first few months after commencing HRT.[2]

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Progestogen intake could be modified as follows:
For cyclical HRT regimens, the dose of progestogen could be increased (e.g. micronised progesterone 300 mg for 12 days a month instead of 200 mg, or switch to a different progestogen) or increase duration of progestogen intake (can take progestogen for 14 days a month or for 21 days out of a 28-day HRT intake cycle).

For continuous combined HRT regimens, the dose of progestogen could be increased (e.g. increase micronised progesterone daily dose from 100 mg to 200 mg daily on continuous basis, or switch to a different progestogen), particularly when combined with higher dose estrogenic regimens.

Those on continuous combined HRT regimens that contain a progestogen in a combined preparation or have a levonorgestrel intrauterine device could have micronised progesterone/ medroxyprogesterone acetate or norethisterone added to their HRT regimen. If breakthrough bleeding occurs following the switch to continuous combined HRT and does not settle after 3-6 months, then the woman can be switched back to a sequential regimen for at least another year.

If women continue to experience ongoing unscheduled bleeding with continuous combined HRT, the HRT regimen could be changed to a cyclical intake of progestogen.

Unscheduled bleeding is higher with continuous combined HRT regimens compared to that with sequential regimens. In addition, with continuous combined regimens, oral continuous combined preparations maybe associated with less breakthrough bleeding compared with transdermal preparations.

Progestogens in HRT: preparations and recommended doses

Micronised progesterone
200 mg orally 12 days/cycle (cyclical)
100 mg PO daily (continuous combined)
Preparations: Utrogestan: 100 mg oral capsule, 200 mg vaginal pessary, Cyclogest 200 mg vaginal pessary, Lutigest 100 mg vaginal pessary, Gepretix 100 mg and 200 mg oral capsules

Dydrogesterone
10 mg for 12-14 days a month (cyclical)
5 mg a day (continuous combined)
2.5 mg a day (low dose continuous combined)

Medroxyprogesterone acetate (MPA)
10 mg for 12 days a month (cyclical)
a minimum of 2.5 mg a day (continuous combined)

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Norethisterone
5 mg for 12 days a month (cyclical) [given that no smaller (1-2 mg) dose stand-alone norethisterone preparations are available in the UK]
0.5-1 mg a day (continuous combined)

Off license use of norethisterone in progestogen only contraceptive pills (e.g. Noriday 3 x tablets of 350 micrograms a day, will provide 1.05 mg of norethisterone) may be considered as an equivalent alternative.

Drospirenone
4 mg (Slynd) is licensed in the UK as a progestogen only contraceptive. It can be used off license as the progestogen component of HRT by taking one active hormone tablet 4 mg daily on a continuous basis (omitting the 4 hormone free pills in the pack).

Desogestrel
Earlier studies have reported that desogestrel 150 micrograms is effective as the progestogen component of HRT with no increase in the risk of endometrial hyperplasia.[33-34] There is lack of evidence on the use of desogestrel 75 micrograms as the progestogen component of HRT.

If desogestrel 75 micrograms is used as contraception in women receiving HRT, it would be recommended to add further progestogen (e.g. Utrogestan 100 mg daily or 200 mg for 12 days a month) to provide adequate endometrial protection.

Dienogest
2 mg can be considered as an option (off license) if other measures have been ineffective.[36]

Levonorgestrel IUD
Can be used for 5 years (Mirena IUD has a license for 4 years in the UK).

NOTE: clinical safety concern regarding progesterones within compounded bioidentical hormone preparations

There are concerns related to the purity, potency and safety of compounded preparations and there is lack of evidence to suggest that the dosage of progesterone used in compounded preparations provides sufficient endometrial protection. The use of such compounded preparations is not recommended.

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