HRT regimens and progestogen doses

1. HRT regimens and progestogen doses

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Unopposed oestrogen increases endometrial cancer risk

The symptom-relieving part of HRT is oestrogen, but giving unopposed oestrogen to women who have not had a hysterectomy significantly increases the risk of endometrial hyperplasia and cancer. We must therefore give a progestogen alongside oestrogen to protect the endometrium and reduce the likelihood of unscheduled bleeding and risk of cancer.

HRT must contain an adequate progestogen to negate this risk

'Combined' HRT formulations generally contain a progestogen dose that is matched with the oestrogen so we don't need to make any dose adjustments. However, increasingly in clinical practice, we are prescribing 'split' regimens in which we give an oestrogen-only preparation with a separate oral or intrauterine progestogen. These regimens enable us to titrate hormone doses and to prescribe medically-safer bioidentical HRT. But this means that as well as prescribing the correct regimen, we must ensure that the patient is receiving adequate progestogen to match the oestrogen dose.

Here's how to ensure this!

In its 2024 guideline on the management of unscheduled bleeding on HRT, the British Menopause Society (BMS) includes some recommendations on optimising HRT prescribing to reduce the risk of bleeding problems on HRT and the risk of endometrial cancer. In this article, we summarise these recommendations and discuss the implications of them for primary care (BMS - management of unscheduled bleeding on hormone replacement therapy).

1.1. Endometrial cancer risk: continuous vs. sequential regimens

The risk of endometrial cancer associated with HRT is dependent on the type of regimen given. If standard (usually licensed) doses of HRT are given:

- Continuous combined regimens are associated with a lower-than-baseline risk of endometrial cancer.
- Sequential combined regimens are associated with:
    - A similar risk of endometrial cancer to baseline for the first 5y of treatment.
    - After 5y, the risk of endometrial cancer increases 3-fold.

If inadequate progestogen is given to match the oestrogen dose, the BMS considers this a major or minor risk factor for endometrial cancer – depending on the duration of inadequate dosing (see table below):

Major risk factors for endometrial cancer	Minor risk factors for endometrial cancer

• BMI ≥40.
• Genetic risk (e.g. Lynch syndrome).
• Unopposed oestrogen use for >6m.
• Prolonged use of sequential regimen (>5y in a woman ≥45y).
• Inadequate progestogen use in a sequential regimen for ≥12m:
  • Tricycling HRT and giving quarterly progestogen.
  • Using <10d of medroxyprogesterone acetate (MPA) or norethisterone per month.
  • Using <12d of micronised progesterone per month.
	• BMI 30–39.
	• Anovulatory cycles (e.g. PCOS).
	• Diabetes mellitus.
	• Unopposed oestrogen use for 3–6m.
	• Inadequate progestogen dose for oestrogen dose (including expired IUS) for >12m.
	• Inadequate progestogen dose in a sequential regimen for 6–12m:
	  • Tricycling HRT and giving quarterly progestogen.
	  • Using <10d of medroxyprogesterone acetate (MPA) or norethisterone per month.
	  • Using <12d of micronised progesterone per month.

1.2. Initiating HRT: sequential or continuous progestogen?

Continuous regimens are safer for the endometrium than sequential regimens. However, perimenopausal women who still have some endogenous ovarian hormone production may develop unscheduled bleeding on continuous regimens. Therefore, when choosing the type of

formulation, we need to balance risk of bleeding with risk of endometrial cancer. The BMS recommends the following:

Start sequential regimen in…	Start a continuous combined regimen in..
• Any woman <55y who has had a period in the past 12m. *Note: where possible, aim to start sequential HRT at the beginning of the natural cycle to synchronise hormonal exposure (i.e. start oestrogen on day 1 and progestogen on day 15 of cycle).*	• Any woman who has been naturally amenorrhoeic for 12m because they are likely to be postmenopausal. • A perimenopausal woman who is amenorrhoeic with hormonal contraception. • An amenorrhoeic woman post-endometrial ablation.
How many days of progestogen will ensure endometrial safety?	
• A minimum of 10d (and 12d for micronised progesterone) per month in sequential regimens. • Evidence suggests that sequential regimens in which progestogens are given for <10d/month are associated with increased risk of endometrial cancer – 3x higher than baseline after 6m of use. • *For ease of dosing, a two-week course each month may be more practical.*	• Every day. *(Note: micronised progesterone is licensed for 25d of a 28d cycle, but BMS guidance recommends a daily dose.)*
Switching from a sequential to a continuous regimen…	

SHOULD be done:

- Within 5y of the start of HRT use.
- By the age of 54y.

MAY be done:

- After 12–18m of HRT use if the woman wishes to try a 'bleed-free' regimen earlier.

1.3. HRT dose matching: oestrogen doses

Due to the limitations of the evidence, the BMS has adopted a pragmatic, opinion-led approach to optimal HRT regimens. The table below is based on the BMS guidance, and categorises oestrogen regimens by dose strength in order to guide appropriate progestogen dose.

Categorisation of oestrogen regimens

IMPORTANT!! The doses in italics are off-licence doses. There is no published evidence supporting the efficacy or safety of off-licence oestradiol doses, nor national or international guidelines endorsing their use. We have included them in the table because they feature in the BMS guidance on management of unscheduled bleeding on HRT.

Formulation	Strength of dose				
	Ultra-low	Low	Standard	Moderate	High
Oestrogel	½ pump	1 pump	2 pumps	3 pumps	4 pu
Patch	12.5mcg	25mcg	50mcg	75mcg	100
Sandrena	0.25mg	0.5mg	1mg	1.5–2.0mg	*3mg*
Lenzetto	1 spray	2 sprays	3 sprays	*4–5 sprays*	*6 sp*
Oral oestradiol	0.5mg	1mg	2mg	*3mg*	*4mg*

Wait! Why are licensed doses of some preparations the equivalent of off-licence doses of others?

The BMS guidance regards 4 pumps of Oestrogel and a 100mcg oestradiol patch (which are both licensed regimens) to be dose equivalent to 6 sprays of Lenzetto and 4mg of oral oestradiol – both of which are twice the licensed dose!

What do the pharmaceutical companies think?

A personal communication with the manufacturers of Lenzetto stated that:

"As 3 sprays per day is the highest recommended dose in the Lenzetto Marketing Authorisation (as in the SmPC), Gedeon Richter cannot recommend the use of more than 3 sprays per day as this would constitute off-licence use and we have

no data to support such usage. No studies have been performed with doses above this dose. The British Menopause Society, as a learned body, are at liberty to recommend doses that they consider appropriate, however Gedeon Richter cannot recommend off-licence usage. HCPs can prescribe application of higher doses at their own responsibility, but the practicalities of applying more than 3 sprays (i.e. to non-overlapping areas of skin) should be considered."

BMS rationale

The BMS guidance has used pharmacokinetics, clinical trials and clinical experience as the basis of its dose categorisation of oestradiol regimens (03-BMS-TfC-HRT-Practical-Prescribing-NOV2022-A.pdf (thebms.org.uk) . However, we should consider that:

- Doses are subject to considerable variation in absorption and metabolism.
- Measuring oestradiol levels is not very accurate.
- Different formulations deliver oestradiol in different ways.
- Clinical response to oestrogen treatment is very individual.

In essence, this is an inexact science… but one which impacts our consultations and progestogen prescribing (see below).

1.4. HRT dose matching: progestogen doses

The BMS recommends the following doses of progestogen to match the different oestradiol regimens.

(Note: off-licence doses are in italics.)

Progestogen	Oestradiol dose			
-	Ultra-low/low	Standard	Moderate	High
52mg IUS	1 device up to 5y of use			
Sequential regimen				
Micronised progesterone	200mg			*300mg*
Medroxyprogesterone acetate	10mg			*20mg*
Norethisterone	*5mg*			
Continuous regimen				
Micronised progesterone	100mg			*200mg*
Medroxyprogesterone acetate	2.5mg	2.5–5.0mg	5mg	10mg
Norethisterone	1mg		*5mg*	

Licensed progestogen regimens

- Medroxyprogesterone acetate is licensed for endometrial protection up to 10mg a day.
- 1mg of norethisterone is adequate for standard doses of HRT.

However, preparations are only available as a 5mg dose which is off-licence for HRT, but endorsed by the BMS.

- The maximum daily licensed dose of micronised progesterone is 200mg in a sequential regimen, but 300mg is recommended by the BMS when given with high-dose oestrogen.

1.5. What is the rationale for using off-licence progestogen regimens?

The evidence

This is limited.

A number of observational studies have reported increased endometrial cancer rates among women using micronised progesterone compared with those using synthetic progestogen. These have raised concerns about the relative efficacy of endometrial protection from micronised progesterone, and led to suggestions that it may be beneficial to use higher doses – especially in conjunction with higher-dose oestrogens (Women & Health, 2020; https://doi.org/10.1080/03630242.2020.1824956).

A 2016 systematic review examined all the data looking at the endometrial safety of micronised progesterone. It included 40 studies involving different doses and types of oestrogen, and varying progesterone doses. Treatment duration ranged from 4m to 5y. Due to the heterogeneity of the data, the authors found it difficult to interpret the findings, but concluded that a dose of 200mg oral micronised progesterone given sequentially for 12–14d of a cycle should provide adequate endometrial protection for up to 5 years of HRT use (Climacteric, 2016;19(4):316).

The British Menopause Society position

Following its review of the evidence, the BMS concluded that:

- There is no evidence that one progestogen is any more effective than another at protecting against endometrial cancer when a woman is using low to moderate doses of oestrogen.
- There is limited evidence regarding the optimal progestogen dose needed for women taking high-dose oestrogen – especially perimenopausal women on sequential regimens.
- The adequacy of progestogen, particularly of micronised progesterone, is uncertain in women on moderate to high-dose oestrogens.
- But all 52mg IUSs have been shown to provide sufficient endometrial protection for all doses of HRT up to 5y of use.

As a result, the BMS has suggested using higher-dose progestogens to match higher-dose oestrogens in order to prevent breakthrough bleeding and reduce endometrial cancer risk.

1.6. Implications of the increased micronised progesterone dose recommendation

While pragmatic, this is quite a controversial recommendation because it is based on a paucity of evidence, rather than actual evidence of harm. This raises some issues:

- It is not clear what effect increased progestogen doses have on other disease risks such as VTE and breast cancer.
- Micronised progesterone has been shown to be a medically-safe

progestogen at licensed doses, but we have no evidence of safety or tolerability at increased doses.

- If prescribing an off-licence progestogen dose alongside a licensed oestrogen regimen, we will need to discuss (and agree) this treatment decision with our patients – which could be confusing to them and time-consuming for us.
- High-dose oestrogen regimens with micronised progesterone are commonly used by our menopausal patients, so increasing the micronised progesterone dose in all these women will potentially have cost implications for the NHS.

What does this mean in practice?

This means that we may be more reluctant to prescribe 100mcg oestradiol patches or to recommend a dose of 4 pumps a day of Oestrogel, unless the woman has an IUS in-situ (and which is in date).

1.7. What about women with progestogen intolerance?

Some women struggle with side-effects from progestogens, and options for these patients are limited. The BMS mentions the following possible options:

- Offer a 52mg IUS.
- Use an off-licence progestogen, e.g. 150mcg of daily desogestrel or 3x Noriday tablets.
- Consideration of hysterectomy.

If these are not suitable or acceptable, and the woman still wishes to continue HRT, the BMS states that:

- A shortened duration of progestogen may be given with informed and documented counselling about endometrial risk.
- There is lack of evidence to support surveillance (6-monthly) ultrasound scanning (*but doesn't stipulate whether it recommends this or not*).

HRT regimens and risk of endometrial cancer

- Continuous combined HRT is associated with a reduced risk of endometrial cancer.
- Sequential combined HRT does not increase the risk of endometrial cancer for the first 5 years of use, but is associated with an increased risk after this time.
- We should ensure that all women are on a continuous combined regimen within 5y of starting HRT, or by the age of 54y.
- In a sequential regimen, a progestogen must be given for a minimum of 10d, and 12d in the case of micronised progesterone.
- When prescribing HRT, we must ensure that the oestrogen dose is balanced by an adequate progestogen dose.

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