Guidelines
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The importance of the progestogenic component of hormone replacement therapy in women with a uterus

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Introduction

The menopause transition is a critical stage in women's health. The oestrogen deficiency that accompanies the menopause is associated with irregular periods, eventual amenorrhoea, and multiple other symptoms—the most common being hot flushes and night sweats, vaginal dryness, mood changes, sexual dysfunction (including loss of libido), memory and concentration changes, headaches, and joint and muscle complaints. Around 80% of women will experience vasomotor symptoms,[1] with most rating these as moderate to severe.[2] An American observational study indicated that the median vasomotor symptom duration is 7.4 years.[3] Furthermore, vasomotor symptoms are independently associated with multiple indicators of elevated cardiovascular risk,[4] and reduction in bone mineral density (BMD).[5]

NICE guidance advises offering hormone replacement therapy (HRT) for vasomotor symptoms after discussing with women the short-term (up to 5 years) and longer-term benefits and risks.[6] However, the management of menopausal symptoms often presents a clinical challenge to prescribers. Concerns about breast cancer risk have contributed to reduced prescribing of HRT in the UK. Initial data from the 2002 Women's Health Initiative (WHI) trial showed an increased risk of breast cancer, albeit not statistically significant, and possible early harm from coronary heart disease (CHD) in women receiving combined oestrogen and progesterone.[7] Subsequently, follow-up data from the same study published in 2013 showed no detrimental effect on CHD.[8] With careful consideration of the risks and benefits, around 1 million women in the UK currently use HRT to manage their symptoms.[6]

Rationale behind progestogen prescribing

Oestrogen alone can be offered to women without a uterus, whereas the addition of a progestogen is required for women with a uterus.[6] A regimen containing bazedoxifene (BZA; a selective oestrogen receptor modulator) combined with conjugated equine oestrogens (CEE) is available as a progestogen-free alternative for use in women with a uterus.[9] Tibolone is a synthetic compound with weak oestrogenic, progestogenic, and androgenic activity, and is also licensed for HRT use in the UK.[10] It may be given to women with low libido, but adverse metabolic effects limit its use.

The association between unopposed oestrogen therapy and endometrial hyperplasia/neoplasia is established.[11] A 20% incidence of endometrial hyperplasia was shown with 1 year of unopposed oestrogen use.[12] Cyclical progestogen given in combination with low-dose oestrogen for 10 days monthly reduced endometrial hyperplasia to placebo rate,[13] and the WHI trial, which used continuous combined HRT, demonstrated a 19% reduction (non-significant) in endometrial hyperplasia compared with placebo.[14]

In some cases, progestogens (in a combined HRT regimen) are prescribed to women without a uterus but with a history of severe endometriosis to prevent symptom reactivation (e.g. pelvic pain), recurrence, and malignant

transformation of endometriotic foci.[15] Despite a lack of high-quality studies, case reports consistently show a predominance of oestrogen-only HRT in women with recurrence of endometriosis and malignancy.[15] As a result, combined preparations are often favoured.[15]

Progestogens currently available for prescription

Broadly speaking, progestogens have one effect in common: the induction of a characteristic effect on the oestrogen-primed endometrium.[16] There are, however, large variations in the myriad other biological effects elicited by different progestogens.[16] The progestogenic activity of any substance also depends on its timing and route of administration. A list of progestogens currently licenced for use in the UK as part of combined HRT and their receptor activities is provided in Table 1.

Progestogens also exhibit antigonadotropic effects, which inhibit ovulation when prescribed for contraceptive use.[16]

Contraindications and side-effects

Specific side-effects depend on the type of receptor activity exhibited by each progestogen, as demonstrated in Table 1. Common side-effects for most progestogens include headache, menstrual cycle irregularities, breast pain, skin reactions, and gastrointestinal discomfort.[17] General contraindications include breast, ovarian, or uterine cancer, a history of blood clots, and liver disease,[17] with specific contraindications for each preparation.

Risks associated with progestogen prescribing

Breast cancer

NICE guidance advises explaining to women around the natural age of menopause that the baseline risk of breast cancer varies according to the presence of underlying risk factors.[6] HRT with oestrogen alone is associated with little or no change in the risk of breast cancer relative to baseline risk, whereas HRT with oestrogen and progestogen can be associated with a slightly increased risk of breast cancer.[6]

NICE guidance reports a baseline population risk of breast cancer of 22.48 per 1000 women over 7.5 years.[6] Follow-up data from the WHI trial demonstrated that, for current HRT users, there were four fewer cases of breast cancer per 1000 women among women using oestrogen alone relative to baseline, although this was not statistically significant.[8] There were five additional cases of breast cancer per 1000 women among women using oestrogen and progestogen relative to baseline.[8] In simple terms, use of combined HRT is associated with approximately one extra case of breast cancer for every 1000 users per year compared with use of oestrogen alone.[8]

Table 1: Progestogens currently licenced for use in the UK as part of combined HRT

Progestogen	Oestrogenic	Anti-oestrogenic	Androgenic	Anti-androgenic	Glucocorticoid	Antimineralocorticoid
Norethisterone	✓	✓	✓	✗	✗	✗
Levonorgestrel/ Norgestrel (including intrauterine devices)	✗	✓	✓	✗	✗	✗
Progesterone	✗	✓	✗	✓	✓	✓
Medroxyprogesterone acetate	✗	✓	✓	✗	✓	✗
Dydrogesterone	✗	✓	✗	✓	✗	✓

In the WHI trial, combined HRT consisted of CEE with medroxyprogesterone acetate (MPA),[7,8] and the same risk may not apply to different types of progestogen. Two cohort studies showed that oestrogen combined with either progesterone or dydrogesterone is not associated with a statistically significantly increased risk of breast cancer.[18,19] This may be because some progestogens reduce proliferation; however, their effects on breast tissue are complex and poorly understood.[18] A case-control analysis by the UK-based General Practice Research Database also demonstrated that use of oestrogen with dydrogesterone is not associated with an increased risk of breast cancer.[20]

Venous thromboembolism

The risk of venous thromboembolism (VTE) is increased by oral HRT relative to baseline population risk.[8] Conversely, epidemiological studies have not identified a risk of VTE above baseline population risk with the use of transdermal HRT.[21–23] This is likely because transdermal delivery avoids first-pass liver metabolism of oestrone (the main metabolite of oral oestradiol) in the liver, which increases thrombin generation.[24]

When defining VTE risk, observational studies have also outlined the importance of the type of progestogen associated with oestradiol.[21] The addition of MPA to oral oestrogen may be associated with an increased risk of VTE, and continuous combined regimes may present a greater risk of VTE than sequential regimes.[25]

The ESTHER study, however, demonstrated no significant association between VTE and micronized progesterone.[21] In addition, a recent case-control study confirmed that transdermal HRT preparations were not associated with VTE risk; conversely, oral HRT increased the risk of VTE, and the highest risk of VTE was evident with CEE combined with MPA.[26] Oral oestradiol used in combination with dydrogesterone was not associated with a significantly increased risk of VTE (Figure 1).[26]

Cardiovascular disease

HRT has the potential to improve cardiovascular risk because of beneficial effects on lipids, vascular function, and glucose metabolism.[27] An updated analysis of the WHI trial showed that initiating oestrogen alone closer to the onset of menopause was associated with lower CHD risk and a reduction in total mortality.[8,28] Randomised controlled trials, observational studies, and meta-analyses consistently support primary prevention of CHD and reduction in overall mortality in women initiating HRT nearer to the onset of menopause. The data suggest that the 'window of opportunity' for reducing CHD and overall mortality is initiation of HRT prior to 60 years of age and/or within 10 years of the menopause.[29]

Lipid profiles

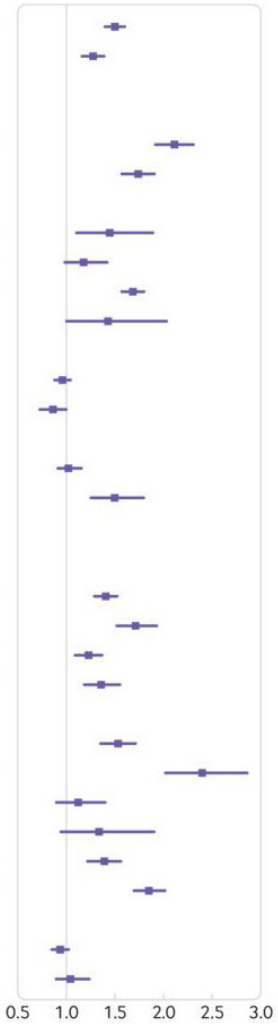
All CEE and CEE/MPA regimens have favourable effects on lipid profiles, including reductions in low-density lipoprotein cholesterol (LDL) and increases in high-density lipoprotein cholesterol (HDL), although triglyceride increases have also been observed with oral therapy.[30] Similarly, an analysis of 248 studies showed that all oestrogen-only regimes raised HDL and lowered LDL.[31] Oral oestrogens raised triglycerides, but transdermal 17β-oestradiol lowered triglyceride levels.[31] This study also showed that progestogens had little effect on oestrogen-induced reductions in total and LDL cholesterol.[31] These positive effects were opposed least by dydrogesterone.[31]

In the SMART trials (a series of phase-3 trials), CEE 0.45 mg/BZA 20 mg and CEE 0.625 mg/BZA 20 mg were shown to have generally positive effects on most lipid parameters for up to 2 years of treatment,[32] although there was some blunting of the oestrogen-induced rise in HDL.

A further study indicated that sequential combinations of either 1 mg or 2 mg 17β-oestradiol with dydrogesterone are associated with long-term favourable changes in serum lipid profile, and there is no evidence that dydrogesterone compromises these 17β-oestradiol-induced improvements.[33]

Figure 1: Adjusted odds ratios for VTE risk with different types of HRT and different doses of oestrogen[26]

Different types of HRT	Odds ratio (95% CI)
Oestrogen only oral HRT	
Conjugated equine oestrogen	1.49 (1.39 to 1.60)*
Estradiol	1.27 (1.16 to 1.39)*
Combined oral HRT	
Conjugated equine oestrogen	
Medroxyprogesterone	2.10 (1.92 to 2.31)*
Norgestrel	1.73 (1.57 to 1.91)*
Estradiol	
Medroxyprogesterone	1.44 (1.09 to 1.89)*
Dydrogesterone	1.18 (0.98 to 1.42)
Norethisterone	1.68 (1.57 to 1.80)*
Norgestrel/drospirenone	1.42 (1.00 to 2.03)
Transdermal HRT	
Estradiol	0.96 (0.88 to 1.04)
Combined estradiol	0.86 (0.73 to 1.01)
Other menopausal therapy	
Tibolone	1.02 (0.90 to 1.15)
Raloxifene	1.49 (1.24 to 1.79)*
Different doses of oestrogen in HRT	
Oestrogen only oral HRT	
Conjugated equine oestrogen ≤0.625 mg	1.40 (1.28 to 1.53)*
Conjugated equine oestrogen >0.625 mg	1.71 (1.51 to 1.93)*
Estradiol ≤1 mg	1.22 (1.09 to 1.37)*
Estradiol >1 mg	1.35 (1.18 to 1.55)*
Combined oral HRT	
Conjugated equine oestrogen ≤0.625 mg, norgestrel	1.53 (1.36 to 1.72)*
Conjugated equine oestrogen >0.625 mg, norgestrel	2.38 (1.99 to 2.85)*
Estradiol ≤1 mg, dydrogesterone	1.12 (0.90 to 1.40)
Estradiol >1 mg, dydrogesterone	1.34 (0.94 to 1.90)
Estradiol ≤1 mg, norethisterone	1.38 (1.23 to 1.56)*
Estradiol >1 mg, norethisterone	1.84 (1.69 to 2.00)*
Transdermal HRT	
Estradiol ≤50 µg	0.94 (0.85 to 1.03)
Estradiol >50 µg	1.05 (0.88 to 1.24)



Odds ratios are adjusted for current use of conjugated equine oestrogen cream, estradiol pessaries, oral progestogen, progesterone cream or vaginal preparations, past use of HRT, smoking status, alcohol consumption, Townsend deprivation fifth (QResearch only), body mass index, comorbidities, recent events, current and past use of antidepressants, antipsychotics, aspirin, oral contraceptives, tamoxifen, and years of data. Cases are matched to controls by age, general practice, and index date. *p<0.01

Adapted from Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ* 2019; **364**: k4810. Reproduced under the terms of the CC BY 4.0 license (**creativecommons.org/licenses/by/4.0/**)

Insulin resistance

Overall, HRT in the form of CEE, oral esterified oestrogens, or transdermal oestrogen—alone or in combination with progestogens—reduces insulin resistance.[34] Although the androgenic progestogen MPA has shown adverse effects on glucose and insulin metabolism,[35] dydrogesterone does not appear to oppose the potentially beneficial effects of oestradiol on insulin.[36]

Choosing the most appropriate progestogen for patients

There is no official UK guidance on choice of progestogen when prescribing combined HRT. The effects of different progestogens on lipids, cardiovascular disease, VTE, glucose metabolism, and risk of breast cancer should therefore be considered by clinicians. Patient preference, side-effect profile, and clinical requirements (e.g. if patient has bothersome bleeding) should also factor in the decision-making process.

Progestogens can be used in continuous or sequential combined HRT regimens. Sequential regimens are most commonly used for women who are perimenopausal or still menstruating.

'Bio-identical' natural progesterone is synthesised from yams, but it is only licensed for HRT use as an oral micronized progesterone capsule. Cohort studies have shown it may not be associated with increased risk of breast cancer, and it is often favoured for this reason.[18,19]

Use of a combination patch or combined oral therapy may be convenient, but it is also limited to the available doses, which may not effectively treat symptoms in individual women. Therefore, separate transdermal oestradiol (patch or gel), in combination with progesterone/an alternative progestogen, may offer greater flexibility to individualise treatment.

The HRT-related risk of serious VTE events increases with age, and is positively associated with obesity and thrombophilia.[25] NICE guidance advises considering transdermal HRT for menopausal women who are at increased risk of VTE, including those with a body mass index over 30 kg/m^2.[6] A suitable choice may therefore be the use of transdermal oestradiol in combination with micronized progesterone in women at increased risk of VTE.

Progestogen-delivering intrauterine devices are often used if contraception is required in conjunction with HRT. This is often the case in perimenopausal women or women with premature ovarian insufficiency, where a spontaneous pregnancy rate of 5% is assumed.

Use of CEE/BZA may be considered in women with progestogen intolerance.

Switching patients to a more suitable progestogen

If transferring from sequential combined HRT, start the new treatment the day after finishing the oestrogen plus progestogen phase. If transferring from continuous combined HRT, start the new treatment at any time.

Summary

HRT is used to alleviate menopausal symptoms and maintain BMD,[6] and may reduce cardiovascular risk, particularly if started early postmenopause.[28] Oestrogen with the addition of a progestogen is required for women with a uterus.[6] Although the inclusion of progestogens in HRT regimens is associated with approximately one extra case of breast cancer per 1000 women per year for current HRT users,[8] micronized progesterone or dydrogesterone may be associated with a lower risk.[18,19] The type of progestogen is also important when considering VTE risk, with micronized progesterone and dydrogesterone appearing to demonstrate the lowest risk.[21] CEE and CEE/MPA regimens have favourable effects on lipids,[30,31] but progestogens have little effect on oestrogen-induced reductions in total and LDL cholesterol.[31] Dydrogesterone does not appear to oppose the potentially beneficial effects of oestradiol on insulin.[36] There

is no current guidance on choice of progestogen for use in HRT in the UK; therefore, individual risk factors, patient preference, and the clinical scenario should to be taken into consideration.

Conflicts of interest

Dr John Stevenson has received grants/research support from Abbott, Mylan, and Pfizer, consulting fees from Abbott and Pfizer, and speaker's honoraria from Abbott, Bayer, Gedeon Richter, Menarini, Mylan, and Pfizer.

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