Review Article

Alfred O. Mueck[1,2] / Thomas Römer[3]

Choice of progestogen for endometrial protection in combination with transdermal estradiol in menopausal women

[1] Department of Women's Health, University Clinical Centre Tuebingen, Tuebingen, Germany, E-mail: Alfred.Mueck@med.uni-tuebingen.de
[2] Department of Gynecological Endocrinology, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China, Phone: +49 7071 298 4801, E-mail: Alfred.Mueck@med.uni-tuebingen.de
[3] Department of Obstetrics and Gynecology, Academic Hospital Weyertal, University Cologne, Cologne, Germany

Abstract:
Transdermal estradiol (TE) application (using gels, patches or a novel spray) is now a preferred route of hormone therapy (HT) in menopausal women, because various risks such as venous thromboembolism, stroke and unwanted hepatic effects can be reduced compared with oral HT. However, in the presence of an intact uterus, concurrent administration of progestogen is needed for endometrial protection. Due to the variety of progestogens available and differences in their clinical effects, the selection of the most appropriate substance and dosing for individual combination therapy can be difficult. This is especially true for TE gels and the novel spray because no fixed combination products are commercially available, meaning all progestogens must be added separately, and even for patches only two transdermal synthetic progestogens are available. The aim of this review was to summarize data on the endometrial effects of the different progestogens and to provide practical recommendations for the choice of progestogen (type and dosing), with a focus on endometrial protection when using TE, especially when using the novel estradiol (E2) spray.

Keywords: endometrial efficacy, endometrial histology, hormone therapy, progestogens, transdermal estradiol spray

DOI: 10.1515/hmbci-2018-0033

Received: May 4, 2018; **Accepted:** June 18, 2018

Introduction

Hormone therapy (HT) is indicated for the treatment of vasomotor symptoms (VMS) and the genitourinary syndrome of menopause caused by reduced estrogen levels. HT helps prevent osteoporosis, colorectal cancer, type 2 diabetes mellitus and possibly also coronary heart disease and Alzheimer's disease if started early in the perimenopause or postmenopause ("window of opportunity"); it can also have a positive effect on quality of life [1], [2], [3], [4], [5], [6].

The effective component of HT for those indications and potential additional benefits is the estrogen component. In hysterecomized women estrogen-only is recommended, i.e. without the addition of a progestogen. Different types of estrogen are available [e.g. conjugated equine estrogens (CEE), synthetic conjugated estrogens, micronized 17β-estradiol (E2), E2-valerate, ethinyl estradiol (EE)] and it can be administered by various routes, such as oral, transdermal, vaginal, intrauterine and as an implant. Long-term unopposed endometrial estrogen exposure increases the risk of endometrial hyperplasia and cancer [7], [8], [9], [10], and consequently progestogens are indicated as part of systemic HT in women with an intact uterus, in order to prevent estrogen-induced endometrial hyperplasia and cancer during estrogen exposure [2], [4], [11].

For several reasons in recent years transdermal estradiol (TE), applied as gels, patches or a novel spray, has been increasingly used for HT. However, progestogen has to be added orally in "free combination" with TE (with the exception of two "combi-patches"), whereas for oral HT "fixed combinations" are generally available and are used in clinical practice.

To facilitate individualized treatment using TE, this paper reviews issues relevant to progestogens used in HT, focusing on endometrial efficacy. Relevant papers, published in English or German, were identified

Alfred O. Mueck is the corresponding author.

via a literature search of the PubMed database. The following sections provide an overview of widely available progestogens, their endometrial efficacy and characteristics. Studies evaluating the use of progestogens in combination with TE preparations will be highlighted. Where possible, the focus is on studies of at least 1 year in duration (reflecting the duration recommended by the European Medicines Agency for the assessment of endometrial safety for HT treatments containing a progestogen) [12]. Practical recommendations on the use of progestogens in combination with TE replacement therapy are provided, based on the literature search and the authors' long-term clinical experience and specialization in the management of menopause.

Possible risks of HT and advantages of TE

According to the Women's Health Initiative (WHI) trial, the only large placebo-controlled trial with relevant clinical endpoints and sufficient statistical power using HT, combined HT was associated with a possible increase in the risk of breast cancer and venous thromboembolism [13], an increased risk of stroke in women starting HT at age 60 years of older, and an increased risk of coronary heart disease in women starting HT at 70 years or older [14] (which in clinical practice is extremely rare). In contrast, in the estrogen-only arm of the WHI trial, only an increased risk of venous thromboembolism was observed, and the risk of breast cancer was found to be significantly decreased [15]. The risk of breast cancer remained decreased after 11 years of follow-up [16], and mortality due to breast cancer remained reduced even after 18-years of follow-up [17].

From these results it becomes clear that the choice of progestogen should take into account the tolerability and risk profile of the various substances. However, in the WHI only one preparation and only one dosage was tested [CEE 0.625 mg/day combined with medroxyprogesterone acetate (MPA) 2.5 mg/day]. In the study, 40% of the study population had severe cardiovascular risk factors (e.g. obesity, hypertension, smoking habits) and two thirds were already older than 60 years (mean 63 years) at the start of HT, and therefore it is not the population seen in general clinical practice. Recently two of the main investigators from WHI indicated that the WHI results for the total population cannot be extrapolated to young women (i.e. those starting HT below 60 years of age) but, regrettably, inappropriate interpretation of WHI results has persisted for more than 10 years [18].

For this reason, and because interventional studies comparing different progestogens are lacking, it is essential to also consider observational data to assist with individualized selection of HT. This is particularly relevant for this review, with its aim of providing advice for the choice of progestogens to add to TE, because only observational data are available for the combination with TE.

According to a variety of observational studies (reviewed in detail elsewhere [7], [19], [20], [21]), TE formulations decrease the risk of venous thromboembolism and stroke while eliciting the same efficacy as oral estrogens in terms of climacteric and urogenital symptoms and other possible benefits described above. In addition, TE can reduce the risk of gallbladder disease, avoid the hepatic first-pass metabolism that occurs with oral estrogens, and is not associated with significant increases in the levels of triglycerides or certain hepatic proteins such as angiotensinogen (a possible advantage in hypertensive patients) or sex hormone-binding globulin (SHBG) (a possible advantage in women with sexual dysfunction) [7], [19], [21].

Sequential and continuous combined HT regimens

Every type of combined HT, irrespective of whether it is administered orally or transdermally, can be performed using two main regimens – sequential-combined (i.e. first estrogen-only followed by estrogen + progestogen) or continuous-combined (i.e. daily estrogen plus progestogen. The sequential-combined regimen can be performed with or without a 1-week break from hormones, although nowadays the regimen without a break is generally recommended to avoid recurrence of climacteric symptoms during the break and other estrogen-withdrawal symptoms such as menstrual migraine. For oral HT, various "fixed combination" preparations are available for use in these regimens, and most studies have evaluated these fixed-combinations rather than "free combinations" (where separate estrogen and progestogen preparations are used). For sequential-combined HT, the progestogen phase should be at least 10 days and preferably 12–14 days per cycle to provide sufficient endometrial protection [19], [22]. Continuous-combined regimens only should be used in postmenopausal patients (this is discussed further in the section on practical recommendations, later in the article).

When using TE as gels or as the novel spray, any progestogen must be added separately as an oral preparation. This is also true for E2-patches with two exceptions: transdermal norethisterone acetate (NETA) and transdermal levonorgestrel (LNG) are available as fixed combinations in so-called "combi-patches". However, because adhesion problems and skin irritation are common with these large patches, and also because of bleeding problems, those "combi-patches" are not often used in clinical practice, and transdermal NETA and transdermal LNG are not available in combination with other forms of TE (i.e. gels or the novel spray).

For practical use approved fixed combination preparations may have some advantages if the choice is oral HT. However, it is difficult to individualize the dosing of the hormonal components, which may be necessary, for example, in case of estrogen- or progestogen-induced side effects, or if bleeding problems occur. Alternatively, a "free combination" has great advantages for the individualization of HT, provided the patient shows good compliance with the use of two preparations, one administered transdermally (gel, patch, novel spray) and one (the progestogen component) generally administered orally (although vaginal application or the LNG-IUD are also options).

Progestogens

Progestogens approved for HT vary between countries, and individual country-specific approval criteria and restrictions should be respected. In general, all progestogens possess the biological potency to transform a proliferated endometrium (caused by estrogen) into a secretory endometrium. However, differences exist between progestogens with respect to their individual transformation dose. Dosing should primarily be aligned with the endometrium effectiveness of the progestogen as assessed in clinical studies. The dosage should not be assessed according to experimental in vitro and/or animal research, as is often described in the literature, because there can be large differences in the "progestational transformation dosage" seen in animals (mostly assessed in the rabbit model) compared to the effect seen in humans in endometrial biopsies [7], [23]. For this reason, in the following sections (and in the tables) only studies with histological investigations performed in women are described.

Classification of progestogens

Progestogens comprise natural progesterone and synthetic progestogens (progestins), all of which exert progestational activity [11], [23]. Progesterone is metabolized rapidly, which is the reason why oral or vaginal administration necessitates a high dosage. In contrast, progestins have structural differences that lead to slower inactivation, meaning they can be used at relatively low doses [11], [23]. The chemical structure of a progestogen influences its hormonal activity via its ability to bind to the progesterone receptor and various other steroid receptors bearing structural similarities to the progesterone receptor, such as the androgen receptor, glucocorticoid receptor and mineralocorticoid receptor [11], [23], [24]. For example, progestins may exert androgenic or antiandrogenic properties, depending on their binding affinity to the androgen receptor and conformational changes that occur after binding [11].

Orally active synthetic progestins can be classified into four main groups based on their structural relationship to progesterone, testosterone, or spironolactone (Figure 1):

- progesterone derivatives
- 19-norprogesterone derivatives
- 19-nortestosterone derivatives
- spirolactone derivative [drospirenone (DRSP)] [11].

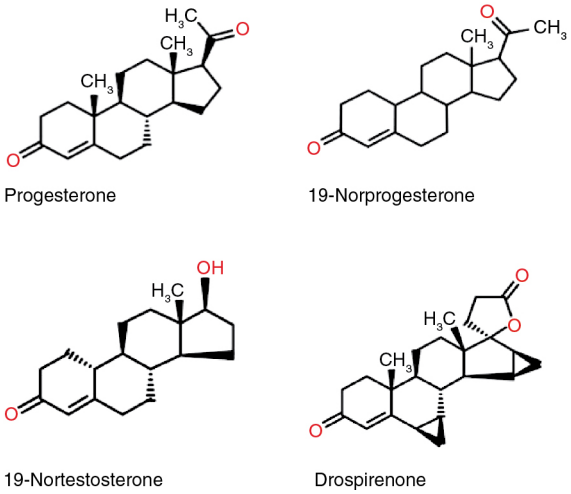

Figure 1: Chemical structure of the four progestogen classes.

Progesterone and progesterone derivatives

Progesterone

Progesterone used as part of combination HT therapy with estrogens is administered orally or vaginally. After oral administration it undergoes extensive metabolism in the gastrointestinal tract and liver, resulting in low bioavailability (<10%) and a half-life of <1–18 h [11], [25], [26]. In the circulation it binds to albumin and corticosteroid-binding globulin [11]. Vaginal administration is associated with greater bioavailability, less variability in serum levels, and slower elimination compared with oral treatment, and the risk of side effects such as sedation may be lower [11], [26]. In addition to its progestogenic effect, progesterone exhibits antiandrogenic activity and exerts an antimineralocorticoid effect, although this is relevant only at high dosages [11].

A systematic review of the effect of micronized progesterone (MP) on the endometrium when used in HT (with any estrogen formulation) concluded that oral MP provides endometrial protection when administered sequentially at a dose of 200 mg/day for 12–14 days/month, and vaginal MP may provide adequate protection when administered sequentially at 45 mg/day for ≥10 days/month or intermittently at 100 mg/day every other day [27]. Data on endometrial effects from clinical trials that specifically evaluated MP in combination with TE and had a duration of at least 1 year are summarized in Table 1. Overall, these studies indicate that when administered at an appropriate dose MP can provide effective endometrial protection in menopausal women receiving TE [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38].

Table 1: Studies evaluating the endometrial effects of micronized progesterone administered in combination with transdermal estradiol for menopausal hormone therapy.

Study	Study design; duration	Number of patients	Hormone therapy	Results
Oral progesterone				
[28]	R, OL; 336 days (12 × 28-day cycles)	100	TE (patch) 50 μg/day + either oral MP 200 mg/day or MPA 10 mg/day or NMA 5 mg/day or DYD 10 mg/day (days 14–25 of 28-day cycle)	No significant difference between groups for median endometrial thickness at baseline or after 12 cycles Endometrial thickness increased significantly ($p < 0.05$) from baseline in all groups, but remained below 6 mm
[29]	R; 336 days (12 × 28-day cycles)	100	TE (patch) 50 μg/day + either oral MP 100 or 200 mg/day or vaginal 100 or 200 mg/day (days 14–25 of 28-day cycle)	No significant difference between groups for median endometrial thickness at baseline or after 12 cycles Endometrial thickness increased significantly ($p < 0.05$) from baseline in all groups (except MP 200 mg/day vaginally) but remained below 6 mm
[30], [31]	R, DB + OL; 18 months (6 months DB + 1 year OL)	336	TE (gel) 1.5 mg/day (days 1–24 per treatment cycle) + either oral MP 200 mg/day or CMA 10 mg/day (days 10–24)	Baseline endometrial histology: atrophic 91.8%, proliferative 4.1%, secretory 3.3% 18-mon endometrial histology: TE + MP: atrophic 27.1%, proliferative 8.3%, secretory 62.5%. TE + CMA: atrophic 19.5%, proliferative 3.7%, secretory 76.8%

[32]	Case series; 5 years	236	TE (gel) 1.5 mg/day for 21 of 28 days (↑ to 3 mg and/or 25 days if required) + MP 200 mg/day on days 14–28 (↑ to 300 mg/day and/or shorten to 10–12 days if required)	Endometrial histology: No evidence of hyperplasia or carcinoma after 5 years. Moderate secretory maturation in 78% of the subgroup who progressed to high TE/high MP and 8% of those who remained on low TE/low MP. No biopsies showed full secretory maturation. Significant negative correlation between duration of MP exposure per cycle and mitotic activity in glandular epithelium
[33], [34]	Non-R, OL; 2 years	51 (1 year) 30 (2 year)	TE (gel) 1.5 mg/day + either oral MP 100 mg/day or vaginal MP 100–200 mg/day on 25 days per calendar month or LNG-IUD (20 µg/day)	Median endometrial thickness (n = 51) did not change considerably in any group after 1 year Endometrial histology (baseline): atrophic or inactive 46/51, mild proliferation 4/51 Endometrial histology (1 year): TE + oral MP: mostly proliferative 8/19, partly proliferative 5/19, secretory 1/19, inactive 4/19. TE + vaginal MP: mostly proliferative 7/14, partly proliferative 1/14, secretory 1/14, inactive 5/14. TE + LNG-IUD: atrophic 12/18, inactive 5/18 Endometrial histology (2 years): TE + oral MP: proliferative 9/10, inactive 1/10. TE + vaginal MP: inactive 3/3. TE + LNG-IUD: atrophic 15/16, partly proliferative 1/16
Vaginal progesterone				
[35]	OL; 1 year	35	TE (patch) 50 µg/day + vaginal MP 45 mg/day twice weekly	Endometrial thickness was significantly greater after 1 year compared with baseline (4.6 vs. 3.6 mm, $p < 0.0005$) Histology showed endometrial atrophy in all cases at baseline; at 1 year, 24 (92.3%) showed atrophy and 2 (7.6%) showed decidualization
[36]	OL; 3 years	30	TE (gel) 1.5 mg/day + vaginal MP 100 mg/day every other day	Mean endometrial thickness decreased significantly from baseline (3.4 mm) to 3 years (2.7 mm, $p < 0.005$). Endometrial histology at 3 years: atrophy in all cases
[37]	OL; 1 year	64	TE (patch) 25 µg/day + vaginal MP 100 mg/day twice weekly	No significant difference in mean endometrial thickness between baseline (2.9 mm) and 1 year (3.5 mm) Endometrial histology assessed in 7 patients because of bleeding; atrophy in all cases

[38]	R; 1 year	60	TE (patch) 50 μg/day + either vaginal MP 100 mg (12 days/month) or oral MPA 10 mg (12 days/month) or transdermal NETA 0.25 mg/day (14 days/month)	Endometrial histology at baseline: TE + MP: atrophic 17/20, proliferative 3/20. TE + MPA: atrophic 16/20, proliferative 4/20. TE + NETA: simple hyperplasia 1/20, atrophic 16/20, proliferative 3/20 Endometrial histology at 1 year: TE + MP: simple hyperplasia 2/20, atrophic 9/20, proliferative 2/20, secretory 7/20. TE + MPA: simple hyperplasia 1/20, atrophic 13/20, proliferative 4/20, secretory 2/20. TE + NETA: simple hyperplasia 3/20, atrophic 11/20, proliferative 5/20, secretory 1/20, simple hyperplasia 1/20. Functional secretory endometrium more common with TE + vaginal MP than other groups ($p < 0.01$). Endometrial atrophy more common with TE + MPA and TE + NETA
[29], [33], [34] See under Oral progesterone (study included both oral and vaginal MP groups)				

CMA, Chlormadinone acetate; DB, double-blind; DYD, dydrogesterone; LNG-IUD, levonorgestrel IUD; MP, micronized progesterone; MPA, medroxyprogesterone acetate; OL, open-label; NETA, norethisterone acetate; NMA, nomegestrol acetate; R, randomized; TE, transdermal estradiol. Studies of at least 1 year's duration (or 12 × 28-day cycles) that reported data on endometrial thickness and/or histology are shown.

One study found histological evidence of endometrial hyperplasia in 10% of recipients of sequential vaginal MP 100 mg/day after 1 year, and a similar proportion of women taking oral MPA 10 mg/day or transdermal NETA 0.25 mg/day [38]. In general, based on practical experience, it is known that the endometrial efficacy of progesterone (especially oral application) can be lower compared with synthetic progestogens (progestins) when used at the recommended dosages of 100–200 mg/day. Because of the good tolerability of this natural progestogen (which is also known from its use in reproductive medicine), dosages up to 400 mg/day can be used in HT with good tolerability in most patients.

Progesterone derivatives

Progesterone derivatives include MPA, chlormadinone acetate (CMA), and cyproterone acetate (CPA). These derivatives have high oral bioavailability (>90%), bind to albumin in the circulation and, especially CMA and CPA, accumulate in fat tissue [11], [24]. For this reason, CMA and CPA have longer elimination half-lives (38–80 h and 54–79 h) than MPA (24–33 h) [11], [24]. CPA and, to a lesser extent, CMA exhibit antiandrogenic activity, whereas MPA exhibits weak androgenic properties [11]. MPA and CPA exert some glucocorticoid effects. None of these three progestins show antimineralocorticoid activity [11].

Endometrial effects of MPA

Most studies assessing the effect of progesterone derivatives on the endometrium have involved MPA, although only a few specifically evaluated MPA in combination with TE (Table 2). A 2-year study (n = 60) found that the incidence of endometrial hyperplasia was substantially lower among women who received TE 0.1 mg/day plus sequential MPA 10 mg/day compared with those who received TE alone (4% vs. 42%) [39]. Another 2-year study involving 100 women who received treatment with TE patches 50 μg/day found that the addition of intermittent MPA 5 mg twice weekly provided similar endometrial protection to a continuous regimen of MPA 2.5 mg/day [40]. Mean endometrial thickness remained less than 5 mm in both groups after 2 years, and the endometrium was atrophic in more than 80% of patients in both groups at baseline and also at the end of the study. Two cases of simple hyperplasia present in the continuous-regimen group at baseline changed to endometrial atrophy after 3 months; one case of simple hyperplasia developed in the intermittent-regimen group during the study [40]. Another study found that in women receiving TE (n = 60), the addition of MPA 10

mg/day for 12 days/month was more likely to result in endometrial atrophy after 1 year, whereas the addition of vaginal MP 100 mg for 12 days/month was more likely to induce a secretory endometrium [38].

Table 2: Studies evaluating the endometrial effects of medroxyprogesterone acetate administered in combination with transdermal estradiol for menopausal hormone therapy.

Study	Study design; duration	Number of patients	Hormone therapy	Results
[38]	R; 1 year	60	TE (patch) 50 μg/day + either transdermal NETA (patch) 0.25 mg/day (14 days/month), vaginal MP 100 mg (12 days/month) or oral MPA 10 mg (12 days/month)	Endometrial histology at baseline: TE + NETA: simple hyperplasia 1/20, atrophic 16/20, proliferative 3/20; TE + MP: atrophic 17/20, proliferative 3/20. TE + MPA: atrophic 16/20, proliferative 4/20 Endometrial histology at 1 year: TE + NETA: simple hyperplasia 3/20, atrophic 11/20, proliferative 5/20, secretory 1/20, simple hyperplasia 1/20. TE + MP: simple hyperplasia 2/20, atrophic 9/20, proliferative 2/20, secretory 7/20. TE + MPA: simple hyperplasia 1/20, atrophic 13/20, proliferative 4/20, secretory 2/20. Atrophic endometrium more common with TE + NETA and TE + oral MPA; functional secretory endometrium more common with TE + vaginal MP ($p < 0.001$)
[39]	R; 96 weeks	60	TE 0.1 mg/day (24.5 days/28-day cycle) alone or + MPA 10 mg (days 13–25)	Hyperplasia incidence: TE + MPA 4% vs. TE monotherapy 42%. All cases were simple, cystic or adenomatous hyperplasia; no atypical hyperplasia or carcinoma Endometrial histology (mid-study + end of study biopsies combined): TE + MPA: insufficient 8/59, atrophy 11/59, proliferative 21/59, secretory 18/59, hyperplasia 1/59. TE monotherapy: insufficient 4/68, atrophy 7/68, proliferative 29/68, secretory 15/68, hyperplasia 13/68
[40]	R, OL; 2 years	100	TE (patch) 50 μg/day + MPA 5 mg twice weekly (intermittent) or 2.5 mg/day (continuous)	Endometrial thickness: mean thickness remained <5 mm in both groups Endometrial histology at baseline: TE + intermittent MPA: atrophy 45/50 (90%), proliferative 5/50 (10%). TE + continuous MPA: atrophy 41/50 (82%), proliferative 7/50 (14%), simple hyperplasia 2/50 (4%) Endometrial histology at 1 year: TE + intermittent MPA: atrophy 31/36 (86%), proliferative 4/36 (11%), simple hyperplasia 1/36 (3%). TE + continuous MPA: atrophic 31/34 (91%), proliferative 3/34 (9%)

MP, Micronized progesterone; MPA, medroxyprogesterone acetate; OL, open-label; NETA, norethisterone acetate; R, randomized; TE, transdermal estradiol. Studies of at least 1 year's duration that reported data on endometrial thickness and/or histology are shown.

Other studies evaluating the endometrial effects of MPA involved its combination with oral estrogen formulations. In the largest study (n = 596), combinations of CEE 0.625 mg/day plus continuous (2.5 mg/day) or

sequential (10 mg/day for 12 days) MPA for 3 years were associated with similar rates of hyperplasia to that seen in a placebo control group; the outcome was also similar for CEE plus sequential MP [41]. Other studies showed that CEE plus continuous MPA 2.5 mg/day tended to promote an atrophic or secretory endometrium after 1–2 years treatment [42], [43], [44], that MPA 5 mg/day and dydrogesterone (DYD) 20 mg/day had similar effects on endometrial cell-cycle kinetics when used in sequential HT with CEE [45], and that the balance between apoptosis and proliferation of endometrial epithelial cells was unchanged after 1 year of continuous combined treatment with CEE plus MPA 5 mg [46]. In studies using other estrogen components, no cases of endometrial hyperplasia were found in postmenopausal women treated for 2 years with E2 valerate 1 or 2 mg/-day plus 2.5 or 5 mg/day MPA (n = 419) [47] or estrone sulfate 1.25 mg/day plus MPA 2.5, 5, or 10 mg/day (n = 568) [48].

Endometrial effects of CMA

The endometrial effects of CMA were reported for one study (Table 3). In this study postmenopausal women (n = 336) received TE 1.5 mg/day, adjuvant administration of oral CMA 10 mg/day from days 10–24 of the 24-day treatment cycle was at least as effective as oral MP 200 mg/day at providing endometrial protection after 18 months [30], [31]. There was no evidence of hyperplasia in either group after 18 months; the endometrium was atrophic in 19.5% of the CMA group vs. 27.1% of the MP group, secretory in 76.8% vs. 62.5% and proliferative in 3.7% vs. 8.3% [31]. Based on the use of CMA in combination with EE for contraceptive pills, endometrial efficacy would be expected using dosages of 2 mg/day. However, as the endometrial proliferating effects of E2 are stronger than those of EE, higher dosages may be needed. This can be recommended due to the general good tolerability of CMA up to 10 mg/day (mostly used for treatment of endometrial hyperplasia) (Mueck, unpublished data).

Table 3: Studies evaluating the endometrial effects of chlormadinone (CMA), dydrogestrone and dienogest (DNG) administered in combination with transdermal estradiol for menopausal hormone therapy.

Study	Study design; duration	Number of patients	Hormone therapy	Results
Chlormadinone (CMA)				
[30], [31]	R, DB (6 months) O-L (12 months)	336	TE (gel) 1.5 mg/day (days 1–24 of treatment cycle plus) + either CMA 10 mg/day (n = 167) or MP 200 mg/day (n = 169) on days 10–24	Endometrial histology at baseline: atrophic 91.8%, proliferative 4.1%, secretory 3.3% Endometrial histology at 6 and 18 months: no evidence of hyperplasia in either group Endometrial histology at 6 months: TE + CMA: atrophic 10.2%, inactive 4.6%, secretory 81.5%, proliferative 3.7%. TE + MP: atrophic 37.3%, inactive 4%, secretory 50.7%, proliferative 8%. Endometrial histology at 18 months: TE + CMA: atrophic 15.8%, inactive 3.7%, secretory 76.8%, proliferative 3.7%. TE + MP: atrophic 20.8%, inactive 6.3%, secretory 62.5%, proliferative 8.3%, other 2.1%
Dydrogestrone				

[49]	O-L (mean 14.9 months)	40	Cyclic sequential HRT: (TE 50 µg/day, days 1–21 plus dydrogesterone 10 mg/day, days 12–24)	Endometrial thickness: No statistically significant difference in endometrial thickness between phase E (6.5±1.6 mm) and phase E/P (6.0±1.7 mm) was observed. In phase 0, compared with phases E and E/P, a statistically significant decrease in endometrial thickness was found (4.1±1.2 mm). Doppler flow impedance parameters of uterine arteries during the different phases of the HRT cycle showed no differences between the phases considered
Dienogest				
[50]	R, DB (1 year)	595	Estradiol valerate 2 mg/dienogest 2 mg (Climodien); estradiol valerate 2 mg/dienogest 3 mg (E2Val 2/DNG 3); or estradiol 2 mg/estriol 1 mg/norethisterone acetate 1 mg [Kliogest]; all once daily for 1 year	Endometial histology: The incidences of endometrial atrophy were similar in all groups. The proportion of patients with endometrial atrophy at the end of the study was similar in the three groups: Climodien (128/141, 90.8%), E2Val 2/DNG 3 (104/119, 87.4%); Kliogest (119/136, 87.5%). No evidence of hyperplasia was observed in any of the three groups
[51]	O-L, multicenter multinational (1 year)	1501	Estradiol valerate 2 mg/dienogest 2 mg (Climodien) for 12 treatment cycles of 28 days for 48 weeks	Endometrial thickness: endometrial thickness remained almost constant, and the incidence of serious endometrial findings was similar to that in untreated women. Mean endometrial thickness (± SD) at baseline was 3.0 (1.5) mm and 24 weeks later it was 3.3 (2.1) mm and after 48 weeks 3.1 (1.5) mm Endometrial histology (n = 115 with endometrial biopsy as a result of the thickness >5 mm or heavy bleeding): two cases of endometrial hyperplasia without adenomatous changes or atypical findings

No studies were performed using TE + chlormadinone acetate. DB, Double-blind; O-L, open-label; R, randomized; SD, standard deviation; TE, transdermal estradiol; E, estrogen phase; E/P, estrogen/progestogen phase; MP micronized progesterone. Studies of at least 1 year's duration that reported data on endometrial thickness and/or histology are shown.

Endometrial effects of CPA

No studies involving TE and CPA were identified; however, one study found that sequential CPA combined with oral E2 valerate provided adequate endometrial protection, with no hysteroscopic evaluations required following endometrial scans after 1 or 2 years of treatment [52].

19-Norprogesterone derivatives

The bioavailability of nomegestrol acetate (NMA) is approximately 60% and the elimination half-life is 35–50 h [11], [24]. In addition to its progestogenic effect, NMA shows some antiandrogenic activity, but no antimineralocorticoid or glucocorticoid activity [53].

In a study involving sequential combination therapy with TE gel 1.5 mg/day for 24 days per calendar month plus NMA 5 mg/day on days 11–24 each cycle, endometrial histology showed a secretory pattern in most women after 6 months, with no hyperplasia [54]. Because NMA is not available for HT in most countries, there is a lack of other studies on endometrial efficacy. However, an oral contraceptive involving a combination of

NMA with 1.5 mg E2 is available, which has a similar profile in terms of efficacy, tolerability and risks compared to other combinations indicated for HT; it may be an alternative option particularly for perimenopausal patients needing contraception and HT [55]. In this combination NMA seems to elicit very strong endometrial efficacy, because in 20–30% of cases no progestogen withdrawal bleeding occurs; however, studies including endometrial biopsies are lacking.

Retroprogesterone (DYD)

DYD is a stereoisomer of progesterone. In addition to a progestogenic effect it has weak antimineralocorticoid effects, but negligible glucocorticoid activity and no androgenic/antiandrogenic effects [11]. It has a bioavailability of approximately 28% and an elimination half-life of 14–24 h [11], [24], [56].

Most studies of the endometrial effects of DYD involved administration in combination with oral E2. However, one small study (n = 40) used TE (Table 3). In this study, the effect of sequential HT with TE 50 μg/day for 3 weeks per month plus DYD 10 mg/day on days 12–24 of each cycle on endometrial thickness during the different phases of the treatment cycle was evaluated [49]. Ultrasound assessments were performed during the different phases of a single treatment cycle after a mean of 14.9 months of treatment. Mean endometrial thickness did not differ significantly between the E2 phase (6.5 mm) and E2/DYD phase (6.0 mm); both were numerically higher than the pretreatment value (3.7 mm). During the week after uterine bleeding, when no hormone was administered, mean endometrial thickness (4.1 mm) was significantly reduced compared with the hormone phases ($p < 0.001$), indicating that DYD was causing regular endometrial shedding [49].

Among trials involving DYD and oral E2, four studies of 1–2 years' duration (n = 27, 151, 188 and 579) showed that sequential combinations of E2 2 mg/day plus DYD 10 or 20 mg/day for 14 days per cycle or E2 1 mg/day plus DYD 5 or 10 mg/day for 14 days provided endometrial progestational success rates of at least 97% (comprising atrophic, inactive or secretory endometrium or insufficient sample for analysis) [57], [58], [59], [60]. Two patients developed simple hyperplasia [58], [60]. Pooled analyses of four or five 6-month and 1-year studies confirmed a low rate of hyperplasia with DYD 5–20 mg therapy; among 236 women treated with sequential DYD 10 mg for more than 1 year, one patient developed simple hyperplasia (0.42%) [61], [62]. One study (n = 446) found a low incidence of hyperplasia (0.27% at 1 year) with a low-dose continuous combined regimen comprising E2 0.5 mg/day plus DYD 2.5 mg/day [63]. DYD has also been evaluated in combination with another oral estrogen, CEE. In this study (n = 241), DYD 20 mg/day and MPA 5–10 mg/day had similar effects on cell-cycle kinetics in the menopausal endometrium when used in sequential HT [45].

In general, DYD should be very useful for combination with TE including the novel spray because it is effective in the endometrium and has good tolerability comparable to progesterone. Thus, dosages up to 20 mg/day can be used while generally maintaining good tolerability in HT [64].

19-Nortestosterone derivatives

Norethisterone acetate (NETA)

After oral administration NETA it is rapidly hydrolyzed to norethisterone (NET), a potent progestin with weak androgenic properties and no antimineralocorticoid or glucocorticoid activity [11], [24]. The bioavailability of NETA/NET is 40–80%, circulating NET binds to SHBG and albumin, and it has an elimination half-life of 8–9.5 h [11], [24].

Data on the endometrial effects of NETA in combination with TE from clinical trials with a duration of at least 1 year are summarized in Table 4. All the studies used transdermal NETA in the combination with TE in the form of so-called "combi-patches", i.e. we did not find published data on endometrial efficacy with oral NETA in combination with TE. Overall, they indicate that transdermal NETA administered continuously at doses of 140–400 μg/day or sequentially at 170–350 μg/day provides endometrial protection during combination therapy with TE 50 μg/day [38], [65], [66], [67]. Hyperplasia did not occur in any patients in three of the studies. In the fourth study (n = 406), the incidence of hyperplasia after 1 year was significantly lower in women receiving E2 plus NETA 140–400 μg/day compared with women who received E2 alone (0.8–1.1% vs. 37.9%, $p < 0.001$) [65]. An atrophic endometrium was common among recipients of continuous NETA regimens [66], [67]. One study found a higher rate of marginal/weakly proliferative endometria with TE 50 μg/day plus transdermal NETA 140 μg/day (21.5%) compared with oral E2 2 mg plus oral NETA 1 mg (4.8%), and a slightly lower rate of secretory endometria (2% vs. 8.1%) [67].

Table 4: Studies evaluating the endometrial effects of transdermal norethisterone acetate or transdermal levonorgestrel administered in combination with transdermal estradiol in the form of "combi-patches" for menopausal hormone therapy.

Study	Study design; duration	Number of patients	Hormone therapy	Results
Transdermal NETA (combi-patch)				
[38]	R; 1 year	60	TE (patch) 50 μg/day + either transdermal NETA (patch) 0.25 mg/day (14 days/mon), vaginal MP 100 mg (12 days/mon) or oral MPA 10 mg (12 days/mon)	Endometrial histology at baseline: TE + NETA: simple hyperplasia 1/20, atrophic 16/20, proliferative 3/20; TE + MP: atrophic 17/20, proliferative 3/20. TE + MPA: atrophic 16/20, proliferative 4/20 Endometrial histology at 1 year: TE + NETA: simple hyperplasia 3/20, atrophic 11/20, proliferative 5/20, secretory 1/20, simple hyperplasia 1/20. TE + MP: simple hyperplasia 2/20, atrophic 9/20, proliferative 2/20, secretory 7/20. TE + MPA: simple hyperplasia 1/20, atrophic 13/20, proliferative 4/20, secretory 2/20. Atrophic endometrium more common with TE + NETA and TE + oral MPA; functional secretory endometrium more common with TE + vaginal MP ($p < 0.001$)
[65]	R, DB; 1 year	625	TE (patch) 50 μg/day alone or + transdermal NETA (patch) 140, 250, or 400 μg/day (continuous)	Endometrial histology: endometrial hyperplasia diagnosed in 0.8% of the TE + NETA 140 group, 1.0% of the TE + NETA 250 group, and 1.1% of the TE + NETA 400 group vs. 37.9% of the TE group ($p < 0.001$)
[66]	R, OL; 1 year	774	TE 50 μg/day + either transdermal NETA 170 or 350 μg/day (continuous or 14 days/cycle) or oral NET 1 mg/day (14 days/cycle) or oral DYD 20 mg/day (14 days/cycle)	Endometrial histology at 1 year: no hyperplasia in any group. Endometrial atrophy more common with continuous transdermal HT (TE + NETA 350: 84%; TE + NETA 170: 66%) than with sequential transdermal HT (32–38%). Estrogen-dominated endometrium: 0.9% and 2.6% with high- and low-dose continuous NETA regimens, 6.2% and 12.5% with high- and low-dose sequential NETA regimens, and 4.5% with oral progestogens
[67]	R, OL; 96 weeks	406	TE (patch) 50 μg/day + transdermal (patch) NETA 140 μg/day (continuous) or oral estradiol 2 mg + oral NETA 1 mg (continuous)	Endometrial thickness at 96 weeks: no clinically significant changes in either group Endometrial histology at 96 weeks: no endometrial hyperplasia or cancer in either group. TE + transdermal NETA: atrophy 73.5%, marginal/weakly proliferative 21.5%, regular/irregular proliferative 1–2%, secretory 2%. Oral estradiol + oral NETA: atrophy 87.1%, marginal/weakly proliferative 4.8%, regular/irregular proliferative 0%, secretory 8.1%
Transdermal LNG (combi-patch)				

[68]	R; 1 year	30	TE 50 µg/day + transdermal LNG 20 µg/day (patch; 2 weeks/cycle; TE 80 µg/day alone for other 2 weeks) vs oral E2 valerate 2 mg/day + oral LNG 75 µg/day	Endometrial thickness did not change in either group
[69]	R, DB; 2 years	212	TE 45 µg/day + either LNG 30 or 40 µg/day (patch) or placebo (patch)	Endometrial thickness: no significant change in any group Endometrial histology: no cases of endometrial hyperplasia or cancer occurred in any group
[70]	R, DB; 1 year	845	TE 45 µg/day + either LNG 15, 30 or 40 µg/day (patch) or TE 45 µg/day (patch)	Endometrial hyperplasia: no cases of endometrial hyperplasia with TE + LNG vs 12.8% with TE alone ($p < 0.001$ for each dose)
[71]	R, OL; 1 year	468	TE 50 µg/day + LNG 10 µg/day (patch; 2 weeks/cycle; TE 50 µg/day for other 2 weeks) or TE 75 µg/day + LNG 15 µg/day (patch; 2 weeks/cycle; TE 75 µg/day for other 2 weeks) or TE 100 µg/day + LNG 20 µg/day (patch; 2 weeks/cycle; TE 100 µg/day for other 2 weeks)	Endometrial hyperplasia (n = 399): two cases of endometrial hyperplasia (one in each of the middle and highest dose groups)

DB, Double-blind; DYD, dydrogesterone; E2, estradiol; IUD, intrauterine device; LNG, levonorgestrel; MP, micronized progesterone; MPA, medroxyprogesterone acetate; OL, open-label; NET, norethisterone; NETA, norethisterone acetate; R, randomized; TE, transdermal estradiol. Studies of at least 1 year's duration that reported data on endometrial thickness and/or histology are shown.

At first glance the use of combi-patches seems to be a reasonable alternative to oral HT, offering the advantages of TE and applying the progestogen within the same application form. However, in practice, the combi-patches are not used very frequently because of adhesion and skin tolerability problems with the large patches, very frequent bleeding problems, and the lack of possibility to change the dosages according to individual patients' needs.

Other studies of the endometrial effects of NETA involved its combination with oral estrogen preparations. Most evaluated oral E2 2 mg plus continuous or sequential oral NETA 1 mg. This regimen commonly resulted in an atrophic endometrium in samples taken after 1–3 years [72], [73], [74]. In a large long-term study, no cases of endometrial hyperplasia or carcinoma were seen among 534 women treated for up to 5 years; at this timepoint the endometrium was unevaluable in 23% of samples, atrophic/inactive in 46%, secretory in 26%, proliferative in 2% and pseudodecidual in 1% [74]. Another study found that the balance between apoptosis and proliferation of endometrial epithelial cells was unchanged after 1 year of continuous use of this combined treatment [46]. A study involving oral E2 1 mg plus a low dose of 0.5 mg oral NETA (n = 246) found no evidence of hyperplasia after 1 year, but the rate of irregular endometrial proliferation with this dose was higher than seen with CEE 0.625 mg plus MPA 2.5 mg (29% vs. 0%, $p = 0.002$) [44]. Studies evaluating oral E2 2 mg plus estriol 1 mg plus oral NETA 1 mg (continuous regimen) found a similar rate of endometrial atrophy and similar endometrial thickness to that seen with E2 valerate 2 mg plus dienogest (DNG) 2–3 mg after 1 year (n = 581) [50], and a similar endometrial thickness to an untreated control group after 5 years (n = 54) [75]. No hyperplasia was seen in 147 specimens obtained during 2402 months of observation of women taking the combination of mestranol 12.5–50 µg/day plus sequential NETA 0.75–1.5 mg [76].

Dienogest (DNG)

In contrast to other nortestosterone derivatives, DNG exerts an antiandrogenic effect [11]. It has no antimineralocorticoid or glucocorticoid activity. Oral DNG has high bioavailability (approximately 95%), does not bind to SHBG or corticosteroid-binding globulin in the circulation, and has a half-life of 9–12 h [11], [24], [77].

The only studies evaluating the endometrial effects of DNG involved a combination with oral E2 valerate (Table 3). After 1 year of treatment, the incidence of endometrial atrophy was similar among women (n = 581) who received E2 valerate 2 mg plus DNG 2 mg (90.8%), E2 valerate 2 mg plus DNG 3 mg (87.4%), and E2 2 mg plus estriol 1 mg plus NETA 1 mg (87.5%), and no endometrial hyperplasia occurred in any group [50]. In a study of 48 weeks' treatment with E2 valerate 2 mg plus DNG 2 mg (n = 1501), endometrial thickness remained largely unchanged and the rate of serious endometrial findings was similar to that seen in untreated women [51]. No studies combining DNG with TE have been published. Although DNG is available as a mono-

substance in most countries, it is indicated only for the treatment of endometriosis. If used "off label" in HT, strong endometrial efficacy can be expected with relatively low dosages.

Levonorgestrel (LNG)

LNG is a potent progestin that exhibits some androgenic activity but no glucocorticoid or antimineralocorticoid activity [11]. After oral administration the bioavailability of LNG is 90–99%. It binds to SHBG and albumin in the circulation and has an elimination half-life of 10–24 h [11], [24]. LNG is often administered via an intrauterine device (IUD) for menopausal HT, with the standard IUD releasing LNG 20 μg/day initially [78]. LNG released from the IUD system accumulates in the endometrium and myometrium.

In most studies involving LNG it was administered via an IUD (20 μg/day) (Table 5). These trials, which had durations of 1–10 years, found no clinically significant changes in endometrial thickness, with endometrial atrophy the most common histological picture, and no evidence of hyperplasia [34], [73], [79], [80]. Studies using LNG-IUD in combination with either transdermal, subdermal or oral E2 support the strong endometrial suppressive effects of LNG and found no evidence of endometrial hyperplasia after 12–22 months [81], [82], [83]. The LNG-IUD also provided effective endometrial protection when used in conjunction with oral E2 valerate 2 mg, inducing endometrial atrophy in most women at the standard dose of 20 μg/day (55/55) and a lower dose of 10 μg/day (46/47), with no endometrial hyperplasia evident after 1 year [78].

Table 5: Studies evaluating the endometrial effects of levonorgestrel-IUD administered in combination with transdermal estradiol for menopausal hormone therapy.

Study	Study design; duration	Number of patients	Hormone therapy	Results
LNG-IUD				
[33], [34]	Non-R, OL; 2	51 (1 year) 30 (2 years)	TE (gel) 1.5 mg/day + either LNG-IUD (20 μg/day) or oral MP 100 mg/day or vaginal MP 100–200 mg/day on 25 days per calendar month	Median endometrial thickness did not change considerably in any group after 1 year Endometrial histology (baseline): atrophic or inactive 46/51, mild proliferation 4/51 Endometrial histology (1 year): TE + LNG-IUD: atrophic 12/18, inactive 5/18. TE + oral MP: mostly proliferative 8/19, partly proliferative 5/19, secretory 1/19, inactive 4/19. TE + vaginal MP: mostly proliferative 7/14, partly proliferative 1/14, secretory 1/14, inactive 5/14 Endometrial histology (2 years): TE + LNG-IUD: atrophic 15/16, partly proliferative 1/16. TE + oral MP: proliferative 9/10, inactive 1/10. TE + vaginal MP: inactive 3/3
[73]	R; 1 year	40	TE (patch) 50 μg/day + LNG-IUD 20 μg/day vs oral E2 2 mg + NETA 1 mg	Mean endometrial thickness: TE + LNG: baseline 2.9 mm, 1-year 4.4 mm. Oral E2 + NETA: baseline 3.3 mm, 1 year 3.0 mm Endometrial histology (1 year): TE + LNG: insufficient 1/15, atrophy 10/15, proliferation 0/15, secretory 4/15. Oral E2 + NETA: insufficient 1/17, atrophy 16/17, proliferation 0/17, secretory 0/17

[79]	R; 1 year	56	TE (patch) 50 μg/day + LNG-IUD 20 μg/day vs. E2 vaginal ring 2 mg + oral MPA (7 days/mon)	Mean endometrial thickness: similar before and after treatment in both LNG (2.9 vs. 2.6 mm) and MPA (3 vs. 2.8 mm) groups Endometrial histology: endometrial proliferation was not observed in either group
[80]	OL; 10 years	153	TE (gel) 1.5 mg/day (90%) or equivalent dose by patch or oral E2 valerate (10%) + LNG-IUD 20 μg/day	Endometrial histology (10 years; n = 148): no endometrial hyperplasia. Dominant picture was endometrial atrophy with stromal decidualization. Scanty or no tissue was obtained in 15/148 (probably profound/extreme atrophy)

E2, Estradiol; LNG-IUD, levonorgestrel intrauterine device; MP, micronized progesterone; MPA, medroxyprogesterone acetate; OL, open-label; NETA, norethisterone acetate; R, randomized; TE, transdermal estradiol. Studies of at least 1 year's duration that reported data on endometrial thickness and/or histology are shown.

Several studies have evaluated the endometrial effects of LNG administered in combination with TE in the form of "combi-patches" for a minimum of 1 year (Table 5). Studies using transdermal LNG at doses of 10–40 μg/day in combination with TE (45–50 μg/day) as combi-patches found no change in endometrial thickness after 1–2 years [68], [84] or endometrial carcinoma after 2 years [68]. Most studies found no evidence of endometrial hyperplasia after 1–2 years [68], [69]; one study reported two cases of hyperplasia among patients receiving E2 and LNG at higher than standard doses [70]. As already described above for the "combi-patches" releasing NETA and E2, these patches are not widely used, because of skin and bleeding problems and difficulties with changing the dosages according to individual patients' needs.

Spirolactone derivative (DRSP)

Drospirenone (DRSP) is a derivative of 17α-spirolactone, with a chemical structure similar to spironolactone. It exerts comparatively low progestogenic activity in the endometrium (10% of that of LNG), has some antiandrogenic activity, and exhibits a strong antimineralocorticoid effect [11]. The oral bioavailability of DRSP is 76–85%, it binds to albumin in the circulation, and has a half-life of approximately 27 h [11].

The only reports on the endometrial effects with DRSP involved its combination with oral E2; in some countries a fixed combination of 1 mg micronized E2 and 2 mg DRSP is available. In a 13-month study of this combination involving 1142 women, the probability of endometrial hyperplasia was 0.007 compared with 0.06 (95% confidence interval 0.043–0.078) with E2 monotherapy (based on incidences of 0.5% and 4%, respectively); nonsignificant differences were seen with DRSP doses of 0.5, 1 and 3 mg [71]. A study using a low-dose combination of E2 0.5 mg/day plus DRSP 0.25 mg/day (to our knowledge not available in any country to date) and comparing it with E2 1 mg plus NETA 0.5 mg (n = 662) found that no women in either group had a biopsy result of 'hyperplasia or worse' after 1 year [85].

These studies indicate that effective endometrial protection could be provided with the use of DRSP. However, to our knowledge, DRSP is not available for use in "free combination" in HT (which would be necessary for combination with TE), so this progestogen is not listed in the Table 1–Table 6.

Table 6: Practical recommendations for the use of progestogens with transdermal estrogen replacement therapy, specifically the novel estradiol spray [86].

Progestogen	Therapeutic scheme	Daily dose (according to number of transdermal E2 sprays per day)			Pharmacology
		One spray	Two sprays	Three sprays	

Progesterone (oral/preferably vaginal)	Sequential Continuous	200 mg 100 mg	200–300 mg 200 mg	300–400 mg 300 mg	Oral progesterone undergoes extensive metabolism in the GI tract and liver, resulting in low bioavailability (<10%) and a half-life of <1–18 h [11], [25], [26]. In the circulation it binds to albumin and corticosteroid-binding globulin [11]. Vaginal progesterone has greater bioavailability, less variable serum levels, and slower elimination compared with oral treatment. Thus, the risk of side effects may be lower [11], [26]. In addition to its progestogenic effect, progesterone exhibits antiandrogenic activity and exerts an antimineralocorticoid effect, although this is relevant only at high dosages [11]
Medroxyprogesterone acetate	Sequential Continuous	5–10 mg (2.5–)5 mg	10–20 mg 5–10 mg	20 mg 10 mg	Progesterone derivatives include medroxyprogesterone acetate (MPA), chlormadinone acetate (CMA), and cyproterone acetate (CPA). These derivatives have high oral bioavailability (>90%), bind to albumin in the circulation and, especially CMA and CPA, accumulate in fat tissue [11], [24]. For this reason, CMA and CPA have longer elimination half-lives (38–80 h and 54–79 h) than MPA (24–33 h) [11], [24]. CPA and, to a lesser extent, CMA exhibit antiandrogenic activity, whereas MPA exhibits weak androgenic properties [11]. MPA and CPA exert some glucocorticoid effects. None of these three progestins show antimineralocorticoid activity [11]
Chlormadinone acetate	Sequential Continuous	2–4 mg (1–)2 mg	4 mg 2–4 mg	4–6 mg 4 mg	
Cyproterone acetate	Sequential Continuous	1 mg 1 mg	2 mg 1–2 mg	3–5 mg 2 mg	
Dydrogesterone	Sequential Continuous	10 mg 5(–10) mg	10–20 mg 10 mg	20 mg 20 mg	Dydrogesterone (DYD) is a stereoisomer of progesterone. It has a bioavailability of approximately 28% and an elimination half-life of 14–24 h [11], [24], [56]. In addition to a progestogenic effect it has weak antimineralocorticoid effects, but negligible glucocorticoid activity and no androgenic/antiandrogenic effects [11]
Norethisterone acetate	Sequential Continuous	1 mg 0.5 mg	1–2 mg 1 mg	2 mg 2 mg	After oral administration norethisterone acetate (NETA) it is rapidly hydrolyzed to norethisterone (NET), a potent progestin with weak androgenic properties and no antimineralocorticoid or glucocorticoid activity [11], [24]. The bioavailability of NETA/NET is 40–80%, circulating NET binds to SHBG and albumin, and it has an elimination half-life of 8–9.5 h [11], [24]

Dienogest	Sequential Continuous	2 mg 2 mg	2–4 mg 2–4 mg	4 mg 4 mg	Oral dienogest (DNG) has high bioavailability (approximately 95%), does not bind to SHBG or corticosteroid-binding globulin in the circulation, and has a half-life of 9–12 h [11], [24], [77]. In contrast to other nortestosterone derivatives, DNG exerts an antiandrogenic effect [11]. It has no antimineralocorticoid or glucocorticoid activity
Levonorgestrel (intrauterine)	Continuous	20 µg	20 µg	20 µg	After oral administration the bioavailability of levonorgestrel (LNG) is 90–99%. It binds to SHBG and albumin in the circulation and has an elimination half-life of 10–24 h [11], [24]. LNG is a potent progestin that exhibits some androgenic activity but no glucocorticoid or antimineralocorticoid activity [11]. LNG is often administered via an intrauterine device (IUD) for menopausal HT, with the standard IUD releasing LNG 20 µg/day initially [78]. LNG released from the IUD system accumulates in the endometrium and myometrium

All progestogens listed are administered orally in combination with the estradiol spray, with the exception of those combinations involving the LNG-IUD and vaginal progesterone.

Novel TE (E2) spray

TE is effective and can offer some advantages over oral administration as described earlier. However, TE applied using patches can be associated with skin irritation, poor adhesion and variable systemic absorption [87], while topical emulsions and various gels registered for menopausal treatment can be associated with skin-to-skin transfer of E2 to other people [88]. In contrast, a novel TE spray causes minimal skin irritation, and no significant transfer of E2 occurs through skin-to-skin contact [89], [90].

As can be seen from the data on endometrial effects described in Table 1–Table 5, in terms of TE, only studies using patches or gels have been reported; to date no studies have tested the endometrial efficacy of different progestogens in combination with the TE spray. However, because the spray can offer some advantages compared with patches or gels and provides an additional option for individualized therapy, physicians may ask if available data on the endometrial efficacy of progestogens when used in combination with TE patches and gels can be extrapolated to the spray. To answer this question, the pharmacology of the novel spray can be summarized as follows.

Phase III study data showed a significant reduction in the frequency of hot flushes in postmenopausal women using one, two, or three sprays of TE spray (1.53 mg/spray) compared to placebo spray, with the reduction evident from 4 weeks onwards [89]. All three dosages were also effective at reducing severity scores. After 12 weeks, systemic E2 delivery rates were approximately 0.021 mg/day, 0.029 mg/day, and 0.040 mg/day with the one, two and three spray doses, respectively [90]. Serum concentrations of E2 and its metabolites estrone and estrone sulfate reached steady state by day 7 or 8 of treatment [91]. Thus, the spray largely shows comparable pharmacology to gels or patches in terms of its efficacy and pharmacokinetic profile. It seems reasonable that data on the endometrial efficacy of the different progestogens (described above and/or in Table 1–Table 5) can be extrapolated to use in combination with the novel TE spray.

The TE spray is indicated for HT of menopausal VMS (hot flushes) using a once-daily continuous regimen [92]. It is advisable to initiate therapy at a low dose (one spray), which is generally an effective dose. However, there are still some open questions about the dose-efficacy relationship using two- or three-spray dosages, because in some patients the maximum efficacy is already reached with two sprays. A possible explanation is that, depending on their skin properties, a high E2 depot can be achieved in some patients with two sprays due to the excellent galenic properties of the spray. This should be considered in the context of practical recommendations, i.e. the progestogen dosage should be not too low when it is added to dosages of two to three sprays.

Table 6 summarizes the practical recommendations of the authors of this review according to our own practice and considering the different pharmacology and tolerability of the progestogens.

Practical recommendations for the use of progestogens with transdermal estrogen replacement therapy

Based on the available data and our long-term clinical experience with treating menopausal women, we offer some recommendations for the use of progestogens in combination with transdermal estrogen therapy in menopausal women with an intact uterus. Current national and international guidelines on the use of HT should be consulted, as should the summary of product characteristics for the different progestogens. The dose and duration of add-on progestogen therapy depends on the estrogen dose being administered. In addition, the metabolic and tolerability profiles of the available progestogens should be considered, and any patient-specific needs should be addressed (e.g. desire for an antiandrogenic effect). In general progesterone and progestogens derived from progesterone are more broadly tolerable compared to other progestins. This is why in the practical recommendations rather large dosages are recommended, especially if higher estrogen dosages are used.

Estrogen should be administered continuously, with progestogen added sequentially for at least 12 (and preferably 14) days per cycle, or continuously (every day), with the latter generally involving a lower dose of the progestogen component. Continuous combined HT should only be used in postmenopausal women; it can cause markedly irregular bleeding in perimenopausal women. Sequential HT in the perimenopause should use a comparatively low estrogen dose and higher progestogen dose because in most patients there is still a very large amount of ovarian E2 production but less or even no progesterone production. With this dosing (i.e. higher relationship of progestogen compared to estrogen dosage), regular progestogen withdrawal bleedings will occur in most cases, which may be especially important for patients who have started HT and have had irregular bleeding due to their perimenopausal stage. If irregular bleeding and/or spotting (which sometimes occurs besides the regular progestogen withdrawal bleedings) are still observed, increasing the estrogen dose is recommended; this can "stabilize" the endometrium and thus avoid breakthrough bleedings.

Sequential therapy on a monthly basis, can also be used in postmenopausal patients, who will mostly continue to have regular progestogen withdrawal bleeds through to an older age (sometimes up to around the age of 60 years). If withdrawal bleedings no longer occur or are becoming weak and/or short-term, a change to continuous-combined HT is recommended, with the aim of achieving amenorrhea at the latest after 4–6 months.

Sequential interval therapy (i.e. progestogen administered at intervals of >1 month) should only be used in exceptional cases (e.g. to reduce the risk of breast cancer in selected patients). In this scenario, a higher progestogen dose should be used (usually double that used with monthly sequential therapy), and frequent ultrasound evaluations of the endometrium should be performed (at least 3-monthly).

Patients at increased risk of endometrial hyperplasia or carcinoma (e.g. due to obesity, anamnestic endometrial hyperplasia, or recurrent bleeding disorders), should generally receive higher recommended progestogen doses.

Appropriate dosing regimens for combination therapy with the novel TE spray plus progestogens are provided in Table 6 [86].

Expert opinion

This review is intended to facilitate the selection of appropriate HT in menopausal women by summarizing the available data on the endometrial effects of progestogens and suggesting dosing regimens for combination therapy using TE as gels, patches or as the novel spray. In contrast to oral combined HT no fixed combinations involving transdermal estrogen are available, except for two combi-patches. So, in women with a uterus the progestogen must be added separately in "free combination", for which (with the exception of vaginal progesterone and the LNG-IUD) only oral progestogens are available. The endometrial effects differ considerably between the various progestogens. The progestogen dosages necessary for secretory transformation during sequential-combined use as well for achieving and/or maintaining endometrial atrophy during continuous-combined use are dependent on the dosage of estrogen. Furthermore, the dosages needed for optimal HT may vary greatly between patients. For this reason, progestogens used in "free combination" with TE can facilitate individualization of treatment, and thus optimize HT.

The novel E2 spray may offer some advantages over other TE preparations; however, to date endometrial efficacy studies using the spray are lacking. Therefore, recommendations for the type and dosage of progestogen

to use in combination with the spray have been derived from data obtained using patches and gels, while taking into consideration the unique pharmacology of the spray and our own experience in clinical practice.

Our "Expert Opinion" may also include a proposal for the best choice of the progestogen type, not only recommendation of the dosages as listed in Table 6. It is our view that in general the more physiological progestogens may be the best first choice, i.e. the natural progesterone or its retro-isomer DYD, not only for reasons derived from an endocrinological point of view but considering their neutral effects in the cardiovascular and metabolic system and the fact that several observational studies as well as experimental research did not find an increased risk of breast cancer up to 8 years of use in hormone replacement therapy. Although progestogen primarily should be added to estrogen to protect the endometrium (in hysterectomized women estrogen-only can be used), main issue for the choice of the progestogen for HT in menopausal women may be the view on the breast cancer risk – patients and doctors mostly fear this risk using hormones. For this reason, this topic has been reviewed by Ruan and Mueck within this journal separately, including a review of extensive own research in terms of breast cancer risk and hormones [93].

Outlook

In future, studies that assess endometrial efficacy when using this novel TE spray combined with different progestogens are needed, to confirm the practical recommendations given within this review.

Highlights

- TE application (gels, patches or a novel spray) is now a preferred route of HT in menopausal women.
- In the presence of an intact uterus, concurrent administration of progestogen is needed for endometrial protection. Selection of the most appropriate progestogen and dosing for individual combination therapy can be difficult, particularly as few fixed combination products are available.
- Progestogen dosing should be aligned with the endometrium effectiveness of the progestogen as assessed in clinical studies including endometrial biopsies.
- The progestogen dose needed for optimal HT can vary greatly between patients.
- Progestogens used in "free combination" with TE (rather than fixed combination products) can facilitate individualization of treatment, and thus optimize HT.
- Practical recommendations are provided for the use of progestogens with transdermal estrogen replacement therapy and specifically with a novel E2 spray.
- Endometrial efficacy studies specifically using the TE spray combined with different progestogens would be of interest.

Acknowledgment

Editorial assistance was provided by Content Ed Net (Germany): here funded by Gedeon Richter.

Author Statement

Research funding: The authors state no funding involved.

Conflict of interest: Both authors have been sponsored by various pharmaceutical companies to speak publicly about hormone therapy, both for and against. Both authors have received research and/or educational grants from various pharmaceutical companies (which do and do not have hormone therapy products) and from non-commercial sources, research councils and charities to conduct research in the field of menopause and hormone therapy.

Informed consent: Informed consent is not applicable.

Ethical approval: The conducted research is not related to either human or animals use.

Author Contributions: TR, AOM: Both authors have worked together in terms of project development, literature research, manuscript writing, and editing.

References

[1] NICE Guidelines. Menopause: diagnosis and management (12 Nov 2015). https://www.nice.org.uk/guidance/ng23/resources/menopause-diagnosis-and-managment-1837330217413.
[2] Baber RJ, Panay N, Fenton A, IMS Writing Group. 2016 Recommendations on women's health and menopause therapy. Climacteric. 2016;19:109–50.
[3] Santen RJ, Allred DC, Ardoin SP, Archer DF, Boyd N, Braunstein GD, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab. 2010;95:s1–s66.
[4] North American Menopause Society. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24:728–53.
[5] Mueck AO. Guidelines for hormone replacement therapy during peri- and postmenopause. Gynäkologische Endokrinologie. 2015;13:270–3.
[6] Utian WH, Woods NF. Impact of hormone therapy on quality of life after menopause. Menopause. 2013;20:1098–105.
[7] Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. Climacteric. 2005;8:3–63.
[8] Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst Rev. 2012;CD000402.
[9] Sjogren LL, Morch LS, Lokkegaard E. Hormone replacement therapy and the risk of endometrial cancer: a systematic review. Maturitas. 2016;91:25–35.
[10] Beral V, Bull D, Reeves G, Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2005;365:1543–5.
[11] Kuhl H. Pharmacology of progestogens. J Reproduktionsmed Endokrinol. 2011;8:157–77.
[12] Committee for Medicinal Products for Human Use (2006). Clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women. CPMP/EWP/021/97 Rev. 1. London: European Medicines Agency, 2006.
[13] Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. J Am Med Assoc. 2002;288:321–33.
[14] Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. J Am Med Assoc. 2007;297:1465–77.
[15] Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. J Am Med Assoc. 2004;291:1701–12.
[16] LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. J Am Med Assoc. 2011;305:1305–14.
[17] Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the women's health initiative randomized trials. J Am Med Assoc. 2017;318:927–38.
[18] Manson JE, Kaunitz AM. Menopause management – getting clinical care back on track. N Engl J Med. 2016;374:803–6.
[19] The North American Menopause Society 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 Hormone Therapy Position Statement of The North American Menopause Society. Menopause. 2017;24:728–53.
[20] L'Hermite M. Bioidentical menopausal hormone therapy: registered hormones (non-oral estradiol ± progesterone) are optimal. Climacteric. 2017;20:331–8.
[21] Pickar JH, Archer DF, Kagan R, Pinkerton JV, Taylor HS. Safety and benefit considerations for menopausal hormone therapy. Expert Opin Drug Saf. 2017;16:941–54.
[22] Ortmann O, Lattrich C. The treatment of climacteric symptoms. Dtsch Arztebl Int. 2012;109:316–23.
[23] Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, Schweppe KW, et al. Classification and pharmacology of progestins. Maturitas. 2003;46:S7–S16.
[24] Stanczyk FZ, Hapgood JP, Winer S, Mishell DR Jr. Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects. Endocr Rev. 2013;34:171–208.
[25] Simon JA, Robinson DE, Andrews MC, Hildebrand JR 3rd, Rocci ML Jr, Blake RE, et al. The absorption of oral micronized progesterone: the effect of food, dose proportionality, and comparison with intramuscular progesterone. Fertil Steril. 1993;60:26–33.
[26] Levine H, Watson N. Comparison of the pharmacokinetics of crinone 8% administered vaginally versus Prometrium administered orally in postmenopausal women. Fertil Steril. 2000;73:516–21.
[27] Stute P, Neulen J, Wildt L. The impact of micronized progesterone on the endometrium: a systematic review. Climacteric. 2016;19:316–28.
[28] Di Carlo C, Sammartino A, Di Spiezio Sardo A, Tommaselli GA, Guida M, Mandato VD, et al. Bleeding patterns during continuous estradiol with different sequential progestogens therapy. Menopause. 2005;12:520–5.
[29] Di Carlo C, Tommaselli GA, Gargano V, Savoia F, Bifulco G, Nappi C. Transdermal estradiol and oral or vaginal natural progesterone: bleeding patterns. Climacteric. 2010;13:442–6.
[30] Pélissier C, Maroni M, Yaneva H, Brin S, Peltier-Pujol F, Jondet M. Chlormadinone acetate versus micronized progesterone in the sequential combined hormone replacement therapy of the menopause. Maturitas. 2001;40:85–94.

[31] Jondet M, Maroni M, Yaneva H, Brin S, Peltier-Pujol F, Pélissier C. Comparative endometrial histology in postmenopausal women with sequential hormone replacement therapy of estradiol and, either chlormadinone acetate or micronized progesterone. Maturitas. 2002;41:115–21.
[32] Moyer DL, de Lignieres B, Driguez P, Pez JP. Prevention of endometrial hyperplasia by progesterone during long-term estradiol replacement: influence of bleeding pattern and secretory changes. Fertil Steril. 1993;59:992–7.
[33] Suvanto-Luukkonen E, Sundström H, Penttinen J, Kauppila A, Rutanen EM. Insulin-like growth factor-binding protein-1: a biochemical marker of endometrial response to progestin during hormone replacement therapy. Maturitas. 1995;22:255–62.
[34] Suvanto-Luukkonen E, Malinen H, Sundström H, Penttinen J, Kauppila A. Endometrial morphology during hormone replacement therapy with estradiol gel combined to levonorgestrel-releasing intrauterine device or natural progesterone. Acta Obstet Gynecol Scand. 1998;77:758–63.
[35] Cicinelli E, de Ziegler D, Galantino P, Pinto V, Barba B, Morgese S, et al. Twice-weekly transdermal estradiol and vaginal progesterone as continuous combined hormone replacement therapy in postmenopausal women: a 1-year prospective study. Am J Obstet Gynecol. 2002;187:556–60.
[36] Cicinelli E, de Ziegler D, Alfonso R, Nicoletti R, Bellavia M, Colafiglio G. Endometrial effects, bleeding control, and compliance with a new postmenopausal hormone therapy regimen based on transdermal estradiol gel and every-other-day vaginal progesterone in capsules: a 3-year pilot study. Fertil Steril. 2005;83:1859–63.
[37] Fernández-Murga L, Hermenegildo C, Tarín JJ, García-Pérez MÁ, Cano A. Endometrial response to concurrent treatment with vaginal progesterone and transdermal estradiol. Climacteric. 2012;15:455–9.
[38] Ferrero S, Gerbaldo D, Fulcheri E, Cristoforoni P. Vaginal micronized progesterone in continuous hormone replacement therapy. A prospective randomized study. Minerva Ginecol. 2002;54:519–30.
[39] Clisham PR, Cedars MI, Greendale G, Fu YS, Gambone J, Judd HL. Long-term transdermal estradiol therapy: effects on endometrial histology and bleeding patterns. Obstet Gynecol. 1992;79:196–201.
[40] Cano A, Tarín JJ, Dueñas JL. Two-year prospective, randomized trial comparing an innovative twice-a-week progestin regimen with a continuous combined regimen as postmenopausal hormone therapy. Fertil Steril. 1999;71:129–36.
[41] Judd HL, Mebane-Sims I, Legault C; The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. J Am Med Assoc. 1996;75:370–5.
[42] AinMelk Y. Comparison of two continuous combined estrogen progestogen regimens in postmenopausal women: a randomized trial. Fertil Steril. 1996;66:962–8.
[43] Hsu SC, Long CY, Yang CH, Wu CH, Chen CH, Liu FI. Cyclooxygenase-2 expression in the endometrium at the end of 2 years' continuous combined hormone replacement therapy. Maturitas. 2003;46:295–9.
[44] Yildirim G, Tugrul S, Uslu H, Pekin O, Eren S. Effects of two different regimens of continuous hormone replacement therapy on endometrial histopathology and postmenopausal uterine bleeding. Arch Gynecol Obstet. 2006;273:268–73.
[45] Chang TC, Chen M, Lien YR, Chen RJ, Chow SN. Comparison of the difference in histopathology and cell cycle kinetics among the postmenopausal endometrium treated with different progestins in sequential-combined hormone replacement therapy. Menopause. 2003;10:172–8.
[46] Dahmoun M, Odmark IS, Risberg B, Karlsson MG, Pavlenko T, Bäckström T. Apoptosis, proliferation, and sex steroid receptors in postmenopausal endometrium before and during HRT. Maturitas. 2004;49:114–23.
[47] Heikkinen JE, Vaheri RT, Ahomäki SM, Kainulainen PM, Viitanen AT, Timonen UM. Optimizing continuous-combined hormone replacement therapy for postmenopausal women: a comparison of six different treatment regimens. Am J Obstet Gynecol. 2000;182:560–7.
[48] Nand SL, Webster MA, Baber R, O'Connor V. Bleeding pattern and endometrial changes during continuous combined hormone replacement therapy. The Ogen/Provera Study Group. Obstet Gynecol. 1998;91:678–84.
[49] Exacoustòs C, Lello S, Caporale E, Minghetti MC, Angelozzi D, Arduini D, et al. Monitoring of hormone replacement therapy in postmenopausal women by transvaginal sonography and color flow doppler: study in different phases of sequential therapy. Fertil Steril. 1999;71:536–43.
[50] Gräser T, Koytchev R, Müller A, Oettel M. Comparison of the efficacy and endometrial safety of two estradiol valerate/dienogest combinations and Kliogest for continuous combined hormone replacement therapy in postmenopausal women. Climacteric. 2000;3:109–18.
[51] Gräser T, Römer T, Wiedey KD, Janaud A. Climodien (estradiol valerate 2 mg plus dienogest 2 mg) is safe and effective in the treatment of postmenopausal complaints. Climacteric. 2001;4:332–42.
[52] Polatti F, Capuzzo E, Viazzo F, Colleoni R, Abbiati I, Nappi RE. Long-term sequential treatment with combined estradiol valerate and cyproterone acetate in early postmenopause. Acta Obstet Gynecol Scand. 1999;78:49–53.
[53] Mueck AO, Sitruk-Ware R. Nomegestrol acetate, a novel progestogen for oral contraception. Steroids. 2011;76:531–9.
[54] Foidart JM, Béliard A, Hedon B, Ochsenbein E, Bernard AM, Bergeron C, et al. Impact of percutaneous oestradiol gels in postmenopausal hormone replacement therapy on clinical symptoms and endometrium. Br J Obstet Gynaecol. 1997;104:305–10.
[55] Ruan X, Seeger H, Mueck AO. The pharmacology of nomegestrol acetate. Maturitas. 2012;71:345–53.
[56] Seeger H, Mueck AO. Effects of dydrogesterone on the vascular system. Gynecol Endocrinol. 2007;23:2–8.
[57] van der Mooren MJ, Hanselaar AG, Borm GF, Rolland R. Changes in the withdrawal bleeding pattern and endometrial histology during 17 beta-estradiol-dydrogesterone therapy in postmenopausal women: a 2 year prospective study. Maturitas. 1994;20:175–80.
[58] Ferenczy A, Gelfand MM. Endometrial histology and bleeding patterns in post-menopausal women taking sequential, combined estradiol and dydrogesterone. Maturitas. 1997;26:219–26.
[59] Ferenczy A, Gelfand MM, van de Weijer PH, Rioux JE. Endometrial safety and bleeding patterns during a 2-year study of 1 or 2 mg 17 beta-estradiol combined with sequential 5–20 mg dydrogesterone. Climacteric. 2002;5:26–35.
[60] van de Weijer PH, Scholten PC, van der Mooren MJ, Barentsen R, Kenemans P. Bleeding patterns and endometrial histology during administration of low-dose estradiol sequentially combined with dydrogesterone. Climacteric. 1999;2:101–9.
[61] Bergeron C, Fox H. Low incidence of endometrial hyperplasia with acceptable bleeding patterns in women taking sequential hormone replacement therapy with dydrogesterone. Gynecol Endocrinol. 2000;14:275–81.

[62] Bergeron C, Ferenczy A. Endometrial safety of continuous combined hormone replacement therapy with 17beta-oestradiol (1 or 2 mg) and dydrogesterone. Maturitas. 2001;37:191–9.
[63] Bergeron C, Nogales FF, Rechberger T, Tatarchjuk T, Zipfel L. Ultra low dose continuous combined hormone replacement therapy with 0.5 mg 17beta-oestradiol and 2.5 mg dydrogesterone: protection of the endometrium and amenorrhoea rate. Maturitas. 2010;66:201–5.
[64] Mueck AO, Seeger H, Bühling KJ. Use of dydrogesterone in hormone replacement therapy. Maturitas. 2009;655:S51–60.
[65] Archer DF, Furst K, Tipping D, Dain MP, Vandepol C. A randomized comparison of continuous combined transdermal delivery of estradiol-norethindrone acetate and estradiol alone for menopause. CombiPatch Study Group. Obstet Gynecol. 1999;94:498–503.
[66] Johannisson E, Holinka CF, Arrenbrecht S. Transdermal sequential and continuous hormone replacement regimens with estradiol and norethisterone acetate in postmenopausal women: effects on the endometrium. Int J Fertil Womens Med. 1997;42:388–98.
[67] Samsioe G, Boschitsch E, Concin H, De Geyter C, Ehrenborg A, Heikkinen J, et al. Endometrial safety, overall safety and tolerability of transdermal continuous combined hormone replacement therapy over 96 weeks: a randomized open-label study. Climacteric. 2006;9:368–79.
[68] Warming L, Ravn P, Christiansen C. Levonorgestrel and 17beta-estradiol given transdermally for the prevention of postmenopausal osteoporosis. Maturitas. 2005;50:78–85.
[69] Shulman LP, Yankov V, Uhl K. Safety and efficacy of a continuous once-a-week 17beta-estradiol/levonorgestrel transdermal system and its effects on vasomotor symptoms and endometrial safety in postmenopausal women: the results of two multicenter, double-blind, randomized, controlled trials. Menopause. 2002;9:195–207.
[70] Sturdee DW, van de Weijer P, von Holst T. Endometrial safety of a transdermal sequential estradiol-levonorgestrel combination. Climacteric. 2002;5:170–7.
[71] Archer DF, Thorneycroft IH, Foegh M, Hanes V, Glant MD, Bitterman P, et al. Long-term safety of drospirenone-estradiol for hormone therapy: a randomized, double-blind, multicenter trial. Menopause. 2005;12:716–27.
[72] Obel EB, Munk-Jensen N, Svenstrup B, Bennett P, Micic S, Henrik-Nielsen R, et al. A two-year double-blind controlled study of the clinical effect of combined and sequential postmenopausal replacement therapy and steroid metabolism during treatment. Maturitas. 1993;16:13–21.
[73] Raudaskoski TH, Lahti EI, Kauppila AJ, Apaja-Sarkkinen MA, Laatikainen TJ. Transdermal estrogen with a levonorgestrel-releasing intrauterine device for climacteric complaints: clinical and endometrial responses. Am J Obstet Gynecol. 1995;172:114–9.
[74] Wells M, Sturdee DW, Barlow DH, Ulrich LG, O'Brien K, Campbell MJ, et al. Effect on endometrium of long term treatment with continuous combined oestrogen-progestogen replacement therapy: follow up study. Br Med J. 2002;325:239.
[75] Dören M, Süselbeck B, Schneider HP, Holzgreve W. Uterine perfusion and endometrial thickness in postmenopausal women on long-term continuous combined estrogen and progestogen replacement. Ultrasound Obstet Gynecol. 1997;9:113–9.
[76] Paterson ME, Wade-Evans T, Sturdee DW, Thom MH, Studd JW. Endometrial disease after treatment with oestrogens and progestogens in the climacteric. Br Med J. 980;280:822–4.
[77] Ruan X, Seeger H, Mueck AO. The pharmacology of dienogest. Maturitas. 2012;71:337–44.
[78] Raudaskoski T, Tapanainen J, Tomás E, Luotola H, Pekonen F, Ronni-Sivula H, et al. Intrauterine 10 microg and 20 microg levonorgestrel systems in postmenopausal women receiving oral oestrogen replacement therapy: clinical, endometrial and metabolic response. BJOG. 2002;109:136–44.
[79] Kalogirou D, Antoniou G, Karakitsos P, Kalogirou O, Antoniou D, Giannikos L. A comparative study of the effects of an estradiol-releasing vaginal ring combined with an oral gestagen versus transdermal estrogen combined with a levonorgestrel-releasing IUD: clinical findings and endometrial response. Int J Fertil Menopausal Stud. 1996;41:522–7.
[80] Wildemeersch D. Safety and comfort of long-term continuous combined transdermal estrogen and intrauterine levonorgestrel administration for postmenopausal hormone substitution – a review. Gynecol Endocrinol. 2016;32:598–601.
[81] Varila E, Wahlström T, Rauramo I. A 5-year follow-up study on the use of a levonorgestrel intrauterine system in women receiving hormone replacement therapy. Fertil Steril. 2001;76:969–73.
[82] Suhonen S, Holmström T, Lähteenmäki P. Three-year follow-up of the use of a levonorgestrel-releasing intrauterine system in hormone replacement therapy. Acta Obstet Gynecol Scand. 1997;76:145–50.
[83] Suhonen S, Haukkamaa M, Holmström T, Lähteenmäki P, Rutanen EM. Endometrial response to hormone replacement therapy as assessed by expression of insulin-like growth factor-binding protein-1 in the endometrium. Fertil Steril. 1996;65:776–82.
[84] Paoletti AM, Pilloni M, Orrù M, Floris S, Pistis M, Guerriero S, Ajossa S, Melis GB. Efficacy and safety of oral and transdermal hormonal replacement treatment containing levonorgestrel. Maturitas. 2002;42:137–47.
[85] Genazzani AR, Schmelter T, Schaefers M, Gerlinger C, Gude K. One-year randomized study of the endometrial safety and bleeding pattern of 0.25 mg drospirenone/0.5 mg 17β-estradiol in postmenopausal women. Climacteric. 2013;16:490–8.
[86] Römer T, Mueck AO. Empfehlungen zur notwendigen Gestagendosis bei Anwendung des transdermalen Estradiol-sprays Lenzetto®. Köln: Gedeon Richter.
[87] Egras AM, Umland EM. The role of transdermal estrogen sprays and estradiol topical emulsion in the management of menopause-associated vasomotor symptoms. Int J Gen Med. 2010;3:147–51.
[88] Taylor MB, Gutierrez MJ. Absorption, bioavailability, and partner transfer of estradiol from a topical emulsion. Pharmacotherapy. 2008;28:712–8.
[89] Buster JE, Koltun WD, Pascual ML, Day WW, Petersen C. Low-dose estradiol spray to treat vasomotor symptoms: a randomized controlled trial. Obstet Gynecol. 208;111:1343–51.
[90] Schumacher RJ, Gattermeir DJ, Peterson CA, Wisdom C, Day WW. The effects of skin-to-skin contact, application site washing, and sunscreen use on the pharmacokinetics of estradiol from a metered-dose transdermal spray. Menopause. 2009;16:177–83.
[91] Morton TL, Gattermeir DJ, Petersen CA, Day WW, Schumacher RJ. Steady-state pharmacokinetics following application of a novel transdermal estradiol spray in healthy postmenopausal women. J Clin Pharmacol. 2009;49:1037–46.
[92] Lenzetto 1.53 mg/spray (transdermal estradiol spray): summary of product characteristics. Budapest: Gedeon Richter, 2016.

[93] Ruan X, Mueck AO. The choice of progestogen for HRT in menopausal women: breast cancer risk is a major issue. Horm Mol Biol Clin Invest. 2018;37. Article ID: 20180019.