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Progestogens for endometrial protection in combined menopausal hormone therapy: A systematic review

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List of abbreviations: CC, Continuously combined EPT; CEE, Conjugated equine estrogens; CMA, Chlormadinone acetate; CPA, Cyproterone acetate; DNG, Dienogest; DRSP, Drospirenone; DSG, Desogestrel; DYD, Dydrogesterone; E2, 17-beta Estradiol; E2V, Estradiol valerate; EE, Ethinyl estradiol; EPT, Estrogen-progestogen-therapy; ET, Estrogen (only) therapy; GSD, Gestodene; HOPE, Women`s Health, Osteoporosis, Progestin, Estrogen study; INN, Medrogestone; IUD, Intrauterine device; LNG, Levonorgestrel; MGA, Megestrol acetate; MHT, Menopausal hormone therapy; MP, Micronized progesterone; MPA, Medroxyprogesterone acetate; NETA, Norethisterone (acetate); NG, Norgestrel; NGM, Norgestimate; NOMAC, Nomegestrol acetate; PEPI, Postmenopausal Estrogen/Progestin Interventions study; RCT, Randomized controlled trial; SEQ, Sequentially-combined EPT; TMG, Trimegstone; WHI, Women's Health Initiative study

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Menopausal women with an intact uterus choosing estrogens for menopausal symptom relief require a progestogen for endometrial protection. The aim of this systematic review was to evaluate the risks of endometrial hyperplasia resp. malignancy with different progestogens used in combined MHT. Overall, 84 RCTs were included. We found that 1) most studies were done with NETA, followed by MPA, MP and DYD and LNG, 2) most progestogens were only available as oral formulations, 3) the most frequently studied progestogens (oral MP, DYD, MPA, oral and transdermal NETA, transdermal LNG) were assessed in continuously as well as in sequentially combined MHT regimens, 4) FDA endometrial safety criteria were only fulfilled for some progestogen formulations, 5) most studies demonstrated endometrial protection for the progestogen dose and time period examined. However, 6) study quality varied which should be taken into account, when choosing a combined MHT, especially if off-label-use is chosen.

Introduction

Menopausal hormone therapy (MHT) is first-line treatment for menopausal symptom relief [1,2]. In women with an intact uterus, estrogens have to be combined with a progestogen for endometrial protection, either in a sequentially or continuously combined regimen [1,2]. Besides the natural micronized progesterone (MP), three types of synthetic progestins are available: progesterone, 19-nortestosterone, and spirolactone derivatives [3]. The aim of this systematic review was to evaluate the risks of endometrial hyperplasia resp. malignancy with different progestogens used in combined MHT depending on their doses, regimens and duration of treatment.

Materials and methods

Information sources and search strategy

Complex literature searches were designed and executed by a medical information specialist (MvG) for the following information sources to identify all potentially relevant documents on the topics: 1) MEDLINE (Ovid) (Ovid MEDLINE(R) ALL (1946 – 29/11/2022)), 2) Embase (Ovid) (1974 – 29/11/2022), 3) Cochrane Library (Wiley) (CDSR, Protocols, CENTRAL (1996 – Present)), 4) CINAHL (EBSCO) (CINAHL with Full Text (1981 – Present)), 5) Web of Science Core Collection (Clarivate) (1900 – Present), 6) ClinicalTrials.gov (NLM) and 7) ICTRP (WHO). An initial search strategy was developed in MEDLINE by a medical information specialist and tested against a list of core references to see if they were included in the search result. After refinement and consultation with the researchers, complex search strategies were set up by the information specialist for each information source based on database-specific controlled vocabulary (index terms) and free-text terms. Synonyms, acronyms and similar terms were included in the free-text search. No database-provided limits have been applied in any of the sources considering study types, languages, publication years or any other formal criteria. All searches were run on 30th November 2022.

The following search concepts were applied: 1. "Endometrium", 2. "Menopause", 3. "Gestagens". Index terms, synonyms, acronyms, similar terms and drug names were used the search in MEDLINE, Embase, CINAHL and the Cochrane Library. The searches in the Web of Science Core Collection and the

trial registers were performed using free text search terms and acronyms only. Studies concerning exclusively animals were excluded from the searches in MEDLINE, Embase and CINAHL by using double-negative search strategies based on the "Humans only" filters by Ovid and the CINAHL Plus RCT filter by Cochrane (https://training.cochrane.org/handbook/version-6/chapter-4-tech-suppl). No other filter strategies were applied. The detailed final search strategies are presented in the Appendix (Supplementary file 1).

Eligibility criteria

Articles were included if women were postmenopausal (natural or surgical menopause) and were taking systemic menopausal hormonal replacement therapy (estradiol (E2) or conjugated equine estrogens (CEE) combined with predefined progestogens such as norethisterone acetate (NETA), dienogest (DNG), dydrogesterone (DYD), mircronized progesterone (MP), drospirenone (DRSP), levonorgestrel (LNG), cyproterone acetate (CPA), medroxyprogesterone acetate (MPA), chlormadinone acetate (CMA)). For inclusion, MHT had to have been administered by oral, transdermal or vaginal route. Duplicates, studies not published in English, German, French or Spanish or studies with no access to the full abstract or full-text were excluded. Only randomized controlled trials in humans were considered.

Study selection and data collection process

All identified records were imported into EndNote, exported as RIS and deduplicated using the online tool Deduklick [4] (MvG). Title and abstract screening was performed by two co-authors (ST, SB) using Covidence and tested against the inclusion criteria. In case of disagreement the full-text article was read to allow for decision making. Then, full-text screening of all identified abstracts was carried out by four co-authors (SB, AE, EP, LW) with each article being checked for relevance twice. Any ambiguity was discussed among all authors. Data extraction from all selected articles was performed by (SB, AE, EP, LW and PS). Results were presented graphically (PRISMA diagram, Fig. 1) and in tabular form (Table 1, supplementary tables 1–8).

Data outcomes

Systematic database searches for the predefined topics yielded a total of 10`288 hits after removing duplicates. After screening of titles and abstracts for these four topics, 130 articles remained. Reviewing the full-text articles with respect to the topic of MHT and endometrium, 84 relevant articles were identified which were included in this paper.

Quality assessment

Co-authors (SB, AE, AK, EP) independently assessed the risk of bias pairwise in each study using the National Institutes of Health (NIH) study quality assessment tool [5]. For any disagreement, a third rater (PS, MvW) was contacted for clarification.

Results

The systematic literature search yielded 84 publications [6–90] (Fig. 1). According to the risk of bias assessment for randomized controlled studies using the National Institutes of Health (NIH) study quality assessment tool [5], 10.7% (9/84) were rated as “good”, 80.9% (68/84) as “fair” and 8.3% (7/84) were rated as “poor” (Supplementary file 2). The results will be presented for each progestogen separately. Table 1 provides an overview of the principle results. Based on [91], systemic estrogen doses are defined as high-, standard-, low- and ultralow-dose.

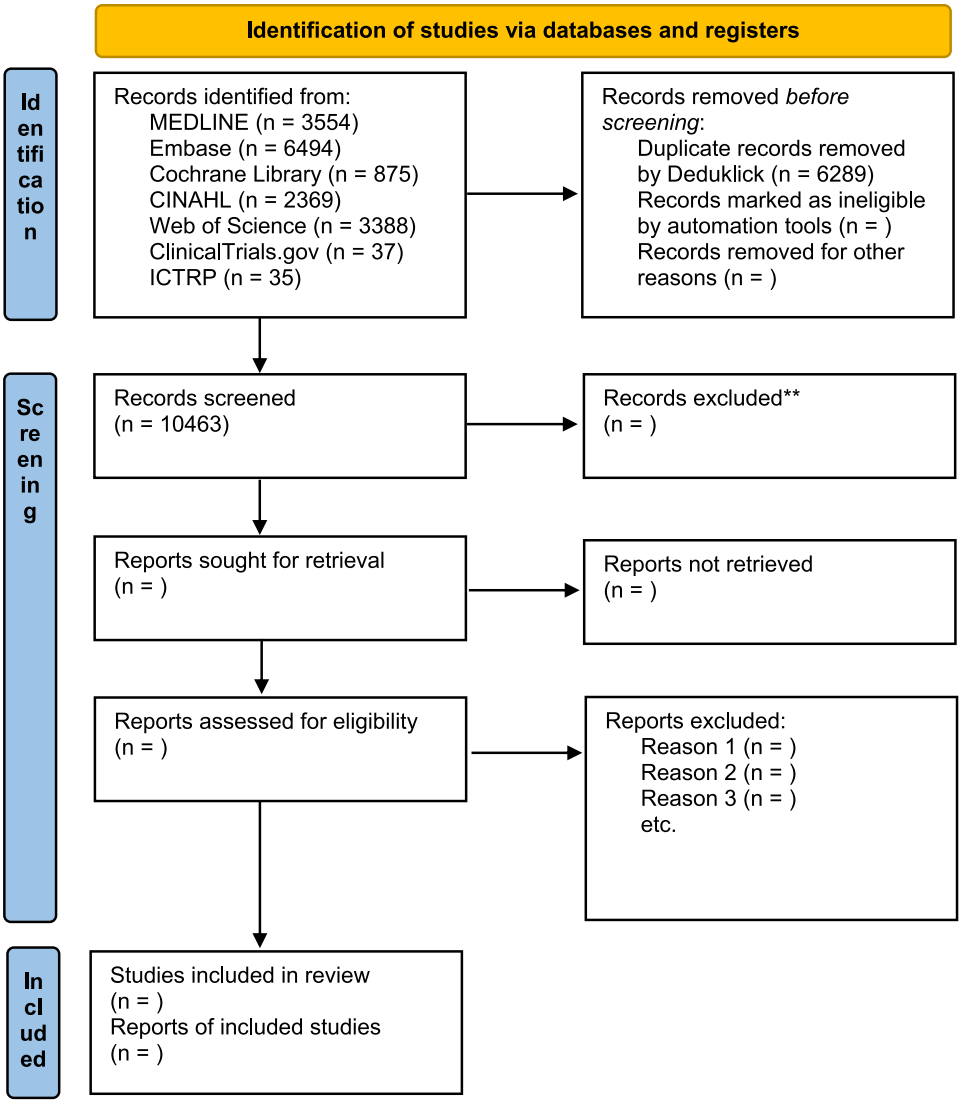

Fig. 1. Prisma Flowchart. **PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only**. **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

Micronized progesterone

Overall, 11 RCTs assessed the endometrial safety of micronized progesterone (MP) in combined MHT (Supplementary table 1). Of those, seven RCTs used oral MP (PEPI) [6], (REPLENISH) [7,8], [9–13], one RCT intramuscular MP [14], one RCT vaginal MP (ELITE) [15], and two RCTs transdermal MP [16,17], respectively. Three RCTs (PEPI) [6], (REPLENISH) [7,8], (ELITE) [15] were placebo-controlled, the remainder head-to-head comparisons using either ET [6,12,16], CMA [11,13], or MPA [6,17] as an active comparator, respectively. Sample sizes ranged from 30 [9] to 1835 (REPLENISH) [7,8] participants all of which were

Table 1
Overview of key results.

Progestagen	Studies (n)	Sample size	Study duration	Progestogen dose	Endometrial safety
Micronized progesterone (MP)					
Oral MP, ccEPT	2	30–1835 postmenopausal women	4 months – 1 year	50 – 200 mg/day	Provided
Oral MP, seqEPT	5	32 – 596 postmenopausal women	3 months – 3 years	100 – 400 mg/day	Provided
Intramuscular MP	1	103 peri- and postmenopausal women	6 months	ccEPT: 15 – 30 mg/month	Provided
Vaginal MP	1	526 postmenopausal women	5 years	seqEPT: 45 mg/day	Not provided
Transdermal MP	2	33–37 postmenopausal women	1 month – 1 year	ccEPT: 40 mg/day seqEPT: 2 × 1.5–4%/day	Provided (cave: insufficient data)
Oral Dydrogesterone (DYD)					
ccEPT	2	277 – 650 postmenopausal women	6 months – 1 year	2.5–20 mg/day	Provided
seqEPT	8	16 – 579 postmenopausal women	6 months – 2 years	2.5–20 mg/day	Provided
Oral Medroxyprogesterone acetate (MPA)					
ccEPT	14	26–16′608 postmenopausal women	3 months – 9 years	1.5 – 5 mg/day	Provided
seqEPT	14	26 – 1724 postmenopausal women	3 months – 3 years	5 – 10 mg/day	Provided
Extended-cycle EPT	2	39–80 postmenopausal women	9 months - 1 year	5 – 10 mg/day	Provided (cave: insufficient data)
Oral Chlormadinone acetate (CMA)					
ccEPT	Not applicable				
seqEPT	2	317 – 336 postmenopausal women	1.5 years	10 mg/day	Provided
Oral Cyproterone acetate (CPA)					
ccEPT	1	75 postmenopausal women	2 years	1 mg/day	Provided (cave: insufficient data)
seqEPT	1	70 postmenopausal women	1 year	0.5 – 2 mg/day	Provided (cave: insufficient data)
Oral medrogestone (INN)					
ccEPT	Not applicable				
seqEPT	1	28	6 months	5 mg/day	Provided (cave: insufficient data)
Oral Nomegestrol acetate (NOMAC)					
ccEPT	Not applicable				
seqEPT	1	36 postmenopausal women	4 months	0.1 – 2.5 mg/day	Provided (cave: insufficient data)
Oral Trimegestone (TMG)					
ccEPT	1	911 postmenopausal women	2 years	0.125 mg/day	Provided
seqEPT	2	634–1218 postmenopausal women	1 year	0.125–0.5 mg/day	Provided
Oral Norethisterone acetate (NETA)					
ccEPT	23	32 – 1741 postmenopausal women	3 months – 2 years	0.2 – 1 mg/day	Provided
seqEPT	8	67 – 1218 postmenopausal women	3 months – 2 years	0.35 – 10 mg/day	Provided
Extended-cycle EPT	1	80 postmenopausal women	1 year	1 mg/day	Provided (cave: insufficient data)
Transdermal Norethisterone acetate (NETA)					
ccEPT	5	228 – 774 postmenopausal women	1 – 2 years	125 – 400 mcg/day	Provided
seqEPT	3	218 – 774 postmenopausal women	1 year	170 – 350 mcg/day	Provided
Intranasal Norethisterone acetate (NETA)					
ccEPT	1	1741 postmenopausal women	1 year	50 – 350 mcg/day	Provided (cave: insufficient data)
seqEPT	Not applicable				

(*continued on next page*)

Table 1 (*continued*)

Progestagen	Studies (n)	Sample size	Study duration	Progestogen dose	Endometrial safety
Oral Levonorgestrel (LNG)					
ccEPT	Not applicable				
seqEPT	2	75 – 123 postmenopausal weomen	2 years	75 mcg/day	Provided (cave: insufficient data)
Intrauterine Levonorgestrel (LNG)					
ccEPT	5	32 – 190 peri- and/or postmenopausal women	1 – 2 years	5 – 20 mcg/day	Provided
seqEPT	Not applicable				
Transdermal Levonorgestrel (LNG)					
ccEPT	1	855 postmenopausal women	1 year	15 – 45 mcg/day	Provided
seqEPT	1	468 postmenopausal women	1 year	10 – 20 mcg/day	Provided
Oral Dienogest (DNG)					
ccEPT	1	581 postmenopausal women	1 year	2–3 mg/day	Provided (cave: insufficient data)
seqEPT	Not applicable				
Oral gestodene (GSD)					
ccEPT	Not applicable				
seqEPT	2	30 postmenopausal women	6 months - 1 year	25 – 50 mcg/day	Provided (cave: insufficient data)
Oral Desogestrel (DSG)					
ccEPT	Not applicable				
seqEPT	2	73–123 postmenopausal women	2 years	150 mcg/day	Provided (cave: insufficient data)
Oral Norgestimate (NGM)					
ccEPT	Not applicable				
seqEPT	1	657 postmenopausal women	1 year	90 – 180 mcg/day	Provided (cave: insufficient data)
Oral Drospirenone (DRSP)					
ccEPT	4	34–1063 postmenopausal women	3 months – 1 year	0.25–3 mg/day	Provided
seqEPT	Not applicable				

Abbreviations: cc = continuously combined, CMA = chlormadinone acetate, CPA = cyproterone acetate, DNG = dienogest, DRSP = drospirenone, DSG = desogestrel DYD = dydrogesterone, EPT = estrogen-progestogen-therapy, GSD = gestodene, LNG = levonorgestrel, MP = micronized progesterone, MPA = medroxyprogesterone acetate, NETA = Norethisterone acetate, NGM = norgestimate, NOMAC = nomegestrol acetate, seq = sequentially combined, TMG = trimegestone.

postmenopausal except for one study that also included perimenopausal women [14]. Study duration ranged from one month [16] to five years [15]. Endometrial safety was assessed by endometrial biopsy at baseline and study end in all but one (ELITE) [15] studies. In ELITE, endometrial biopsies were performed if sonographic endometrial thickness was > 5 mm, or in cases of abnormal uterine bleeding. Four studies applied MP in a continuously combined MHT regimen (REPLENISH) [7,8,9,14,17], whereas seven studies used a sequentially combined MHT regimen (PEPI) [6], (ELITE) [15], [10–13,16], respectively. Estrogen components were either oral CEE, oral E2, transdermal E2, or intramuscular E2 at either high-dose [10], standard-dose [6,9,11,12,16,17], low-dose [7,8,13,15], or ultralow-dose [7,8], respectively. In studies using oral MP in a continuously combined MHT regimen, daily MP doses ranged from 50 mg/day (REPLENISH) [7,8,9], 100 mg/day (REPLENISH) [7,8,9] to 200 mg/day [9]. In the first REPLENISH publication [7], no endometrial hyperplasia was reported. However, in the second REPLENISH publication [8], there was one case of endometrial hyperplasia. In the third RCT [9], there were no cases of endometrial hyperplasia. Similarly, there were no cases of endometrial cancer [7–9]. In studies using oral MP in a sequentially combined MHT regimen, daily MP doses ranged from 100 mg/day [12], 200 mg/day [6,10–13], 300 mg/day [10,12] to 400 mg/day [12]. In the PEPI study [6], there were six cases of endometrial hyperplasia in the group of women receiving MP. However, overall, women with estrogen-progestogen-therapy (EPT) regimens had similar rates of endometrial hyperplasia as women with placebo ($p = 0.16$), and there were no cases of endometrial cancer in any EPT group. The remaining RCTs did not report any cases of endometrial hyperplasia or cancers [6,10–13] (exception: one case of endometrial hyperplasia reported by [12]). The only RCT using intramuscular MP applied 15 mg, 20 mg, or 30 mg MP per month in a continuously combined MHT regimen and did not find any cases of endometrial hyperplasia or cancer [14]. The only RCT using vaginal MP applied 45 mg/day in a sequentially combined MHT regimen (ELITE) [15]. Here, women in the active treatment group had significantly more endometrial biopsies and a higher rate of endometrial hyperplasia (12.7%) compared to placebo (3.1%) with a significant treatment group difference of 9.6%. In addition, three cases of endometrial cancer were reported, two in the active treatment group (incidence 0.8%), and one in the placebo group (incidence 0.4%). Transdermal MP was either applied at 2 × 1.5%/day, or 2 × 4%/day in a sequentially combined MHT regimen [16], or 40 mg/day in a continuously combined MHT regimen [17]. There were no cases of endometrial hyperplasia or cancer reported.

Progesterone derivatives

Dydrogesterone

Overall, 10 original studies [18–27], and one meta-analysis [92] assessed the endometrial safety of oral dydrogesterone (DYD) in combined MHT (Supplementary table 2). All but one (prospective cohort) study [19] were RCTs. Of the RCTs, only one was placebo-controlled [22]. Sample size ranged from 16 [26] to 650 [18] postmenopausal women. Study duration ranged from six months [18,20,25] to two years [22,24]. Endometrial safety was assessed by endometrial biopsy at baseline and study end in all studies. In two studies, DYD was applied in a continuously combined MHT regimen [18,19], whereas eight studies used a sequentially combined MHT regimen [20–27]. In the first, only E2 was used as estrogen component, either in standard- [18], or low-dose [18,19]. In the latter, E2 or CEE were used as estrogen component, either in high- [26], standard- [20,21,23–25], or low-dose [22,27]. In studies using a continuously combined MHT regimen, daily DYD doses ranged from 2.5 mg [18], 5 mg [18,19], 10 mg [18], 15 mg [18] to 20 mg [18]. Overall, three cases of endometrial hyperplasia were reported (E2 2 mg/DYD 2.5 mg [18], E2 2 mg/DYD 5 mg [18], E2 1 mg/DYD 5 mg [19]), corresponding to an endometrial hyperplasia incidence rate of 0.4% [19], and 0.6% [18], respectively. No endometrial cancer was diagnosed. In studies using a sequentially combined MHT regimen, DYD doses ranged from 5 mg [20,22,27], 10 mg [20,22–27], 15 mg [20], to 20 mg [20–22,26], respectively. Overall, four cases of endometrial hyperplasia were reported (E2 2 mg/DYD 5 mg [20], E2 2 mg/DYD 20 mg [20], CEE 1.25 mg/DYD 10 mg [26], E2 1 mg/DYD 5 mg [27]), corresponding to an endometrial hyperplasia incidence rate of 0.66% [27], and 0.69% [20], respectively. In one study [22], three cases of endometrial cancer were reported (0.68%) (E2 1 mg/DYD 5 mg, 2x E2 2 mg/DYD 20 mg). However, they were considered to be pre-existent. Based on a meta-analysis [92] investigating oral E2 at 2 mg/day sequentially combined with DYD at 10 mg/day for 14 days per 28-day cycle in 236 women treated for at least one year, endometrial safety was rated to be good, as

there was only one case of simple hyperplasia (success rate: 99.61%; lower limit of one-sided 95% CI 98.16) and no case of endometrial cancer.

Medroxyprogesterone acetate

Overall, 28 RCTs [17,21,23,28–51] assessed the endometrial safety of oral medroxyprogesterone acetate (MPA) in combined MHT (Supplementary table 3). Study designs were RCTs in all but one study with only partial randomization [47]. Of RCTs, 10 were placebo-controlled [6,28,31,32,36,39,40,45,47,51], the remainder were head-to-head comparisons. Of placebo-controlled RCTs, three were analyses of the WHI [28,32,45], two of the Women's HOPE [39,51], and one of the PEPI [6], respectively. Sample size ranged from 26 [41] to 16′608 (WHI) [28,32,45] postmenopausal women. Study duration ranged from to three months [29] to nine years [34]. Endometrial safety was assessed by endometrial biopsy at baseline and study end in all but two [32,40] studies. 17 studies/analyses (WHI) [28,32,45], (Women's HOPE) [39,51], (PEPI) [6], [17,29,30,33–35,37,41,46,49,50] used MPA at either 1.5 mg/day, 2.5 mg/day or 5 mg/day in a continuously combined MHT regimen. 14 studies (PEPI) [6], [21,23,29,31,36,38,40–44,47–49] used MPA in a sequentially combined MHT regimen at either 5 mg/day [21,29,38,40,42,49] or 10 mg/day [6,21,23,31,36,41,43,44,47–49] during 10 days [31,36,41,44,47], 12 days [6,29,38,43], or 14 days [21,23,42,48,49] per month/cycle, respectively. In two studies, MPA at either 5 mg/day [40] or 10 mg/day [48] was used in an extended-cycle regimen, e.g., either for 13–14 days per three months/cycles [40,48], or for 28 days per three months/cycles [48], respectively. Estrogen types applied were either oral CEE [6,17,21,23,28,29,32,35,39–41,45–51], oral E2(V) [30,31,33–37,42,43,50], transdermal E2 [38,44], or oral ethinylestradiol (EE) [47]. Estrogen dosages were either standard-dose [6,17,21,23,28–51], or low-dose [30,34,35,39,50,51], respectively. As active comparators, either ET (Women's HOPE) [39,51] (PEPI) [6], [49], or MHT containing other progestogens such as oral NETA [30,35,37,43,47,50], oral DSG [31,36], oral DYD [21,23], oral LNG [36], oral Medrogestone [38], oral MP [6], transdermal MP [17], transdermal NETA [44], or LNG-IUD [42] were used. The majority of studies did not report any cases of endometrial hyperplasia or cancer for MHT containing MPA based on endometrial biopsies throughout the study [17,23,29–31,33–42,46,47,50]. The WHI reported a nonsignificant reduction of endometrial cancer risk by MHT containing MPA in a continuously combined regimen [28,32,45] which became significant when considering the combined intervention and postintervention period (HR 0.65, 95% CI 0.48–0.89) [32]. Endometrial cancer mortality remained unchanged [32,34]. A minority of studies reported few cases of endometrial hyperplasia for MHT containing MPA [6,21,43,44,48,49,51]. Thus, the incidence of endometrial hyperplasia was low (0.33% [43], 1.3% [44]). In PEPI, women administered one of the three EPT regimens had similar rates of hyperplasia as those given placebo [6]. MPA dosage was suggested to have an impact as the difference between lower-dose MPA (ccEPT: 2.5 mg/day, seqEPT: 5 mg) and higher-dose (ccEPT: 5 mg/day, seqEPT: 10 mg) approached statistical significance ($p = 0.06$) [49].

Chlormadinone acetate

Overall, two 1.5-year RCTs [11,13] assessed the endometrial safety of oral chlormadinone acetate (CMA) at 10 mg/day in sequentially combined MHT in 317 [11] or 336 [13] postmenopausal women (Supplementary table 4). E2 at standard-dose was either applied orally or transdermally. In both studies, the active comparator was oral MP at 200 mg/day. There was no case of endometrial hyperplasia or cancer.

Cyproterone acetate

Overall, two original studies [31,52] assessed the endometrial safety of oral cyproterone acetate (CPA) in combined MHT (Supplementary table 4). One was a placebo-controlled RCT [31], the second one a head-to-head comparison RCT [52]. Sample size ranged from 70 [52] to 75 [31] postmenopausal women. Study duration was either one year [52] or two years [31]. Endometrial safety was assessed by endometrial biopsy at both, baseline and study end [52], or at study end only [31], respectively. CPA was either used in a continuously combined MHT regimen at 1 mg/day [31], or in a sequentially combined MHT regimen at 0.5 mg/day, 1 mg/day or 2 mg/day for 10 days each [52]. Oral E2 was either standard-dose [31,52] or low-dose [52]. One study chose oral LNG as active comparator [31]. There was no case of endometrial hyperplasia or cancer.

Medrogestone

One 6-month, head-to-head comparison RCT [38] assessed the endometrial safety of oral medrogetone (INN) in combined MHT in 28 postmenopausal women (Supplementary table 4). Women were treated with standard-dose E2 which was sequentially combined with either MPA or INN for 12 days. There were no cases of endometrial hyperplasia or cancer reported.

Nomegestrol acetate

One 4-month, head-to-head comparison RCT [53] assessed the endometrial safety of oral nomegestrol acetate (NOMAC) in combined MHT in 36 postmenopausal women (Supplementary table 4). Women were treated with E2 implants at varying dosages which was sequentially combined with NOMAC at either 0.5 mg/day, 1.0 mg/day or 2.5 mg/day for 12 days. There were no cases of endometrial hyperplasia or cancer reported.

Trimegestone

Overall, three RCTs [54–56] assessed the endometrial safety of oral trimegestone (TMG) in combined MHT (Supplementary table 4). All studies were RCTs with a head-to-head comparison design. Sample size ranged from 634 [56] to 1218 [55] postmenopausal women. Study duration ranged from one year [55,56] to two years [54]. Endometrial safety was assessed by endometrial biopsy at baseline and study end in all studies. TMG was either used in a continuously combined MHT regimen at 0.125 mg/day [54], or in a sequentially combined MHT regimen at 0.125 mg/day [55], 0.25 mg/day [55], or 0.5 mg/day [56] for 14 days, respectively. Oral E2 was either low-dose [54,55], or standard-dose [56]. As active comparator, MHT containing other progestogens such as oral NETA [54,55] or NG [56] were chosen. In total, nine cases with endometrial hyperplasia were reported for 1-year MHT containing oral TMG in a sequentially combined regimen [55,56], but not for oral TMG in a continuously combined 2-year MHT regimen [54]. The corresponding incidences of endometrial hyperplasia were 1.08% [55], or 1.9% [56], respectively. There were no cases of endometrial cancer reported upon use of oral TMG in combined MHT.

19-nortestosterone derivatives

Norethisterone and norethisterone acetate (NET(A))

Overall, 29 original studies [30,35,37,43,47,50,54,55,57–77] assessed the endometrial safety of oral norethisterone (acetate) (NET(A)) in combined MHT (Supplementary table 5). Study designs were RCTs in all but one study with only partial randomization [47]. Of RCTs, six were placebo-controlled [47,58,64,65,67,73], the remainder were head-to-head comparisons. Sample size ranged from 32 [66] to 1218 women [55], or was not provided [77]. Included women were postmenopausal except for one study that included perimenopausal women only [57]. Study duration ranged from three months [67,77] to two years [37,43,54,57,58,62,65,67,70]. Endometrial safety was assessed by endometrial biopsy at baseline and study end in all but three studies [62,64,73]. In most studies (n = 23/29) [30,35,37,47,50,54,58,60–73,75,76], oral NETA was either used at 0.2 mg/day, 0.25 mg/day, 0.5 mg, or 1 mg/day in a continuously combined MHT regimen. Eight RCTs [43,55,57–59,65,74,77] used oral NETA in a sequentially combined MHT regimen at either 0.35 mg/day [58], 0.5 mg/day [59], 0.7 mg/day [58], 0.75 mg/day [59], 1 mg/day [43,55,57,59,65,74,77], 2.5 mg/day [77], 5 mg/day [77], or 10 mg/day [77] during 10 days [43,57,58,65,74,77], or 12 days [55,59] per month/cycle, respectively. In one study, oral NETA at 1 mg/ was used in an extended-cycle regimen, e.g. for 10 days per three months [74]. Estrogen types applied were either oral CEE, oral E2(V), transdermal E2, oral EE, or oral piperazine estrone sulfate. Estrogen dosages were either high-dose [77], standard-dose [30,37,43,54,57–59,61,62,64–66,68,70–72,74,75], low-dose [35,50,54,55,60,62,63,69,72,75], or ultralow-dose [73], respectively. As active comparators, either estrogen only therapy (ET) [63,67], or MHT containing other progestogens such as oral MPA (the majority), oral TMG [54,55], oral DRSP [60], oral DNG [61], oral NGM [68], oral MGA [71], or LNG-IUD [57,66] was used. The majority of studies (n = 25/29) did not report any cases of endometrial hyperplasia or cancer for MHT containing oral NETA based on endometrial biopsies throughout the study. Three studies reported very few cases of endometrial hyperplasia [63,75,76] resulting in an incidence of

endometrial hyperplasia of equal or less than 1% [63,76]. One study reported one case of endometrial cancer [55].

Eight original studies [44,69,70,75,78–81] assessed the endometrial safety of transdermal NETA in combined MHT (Supplementary table 5). All studies were RCTs of which only one was placebo-controlled [79], the remainder were head-to-head comparisons. Sample size ranged from 218 [44] to 774 [80,81] postmenopausal women. Study duration was one year except for one study (two years) [70]. Endometrial safety was assessed by endometrial biopsy at baseline and study end. In studies using a continuously combined MHT regimen, transdermal NETA was used in varying dosages ranging from 125 mcg/day [69,75,79], 140 mcg/day [70,78], 170 mcg/day [80,81], 250 mcg/day [75,78], 350 mcg/day [80,81] to 400 mcg/day [78]. Three studies used transdermal NETA in a sequentially combined MHT regimen at either 170 mcg/day [80,81], 250 mcg/day [44], or 350 mcg/day [80,81] for 14 days each [44,80,81]. E2 was exclusively applied transdermally at standard-dose (50 mcg/day) except for three studies that used transdermal E2 at low-dose (25 mcg/day) [69,75,79]. Most head-to-head comparison RCTs compared different transdermal NETA dosages to each other, or transdermal to oral NETA. Only one study chose estrogen only therapy (ET), or MHT containing oral MPA as active comparators [78]. Half of studies [69,70,80,81] did not report any cases of endometrial hyperplasia. The other four studies [44,75,78,79] reported very few cases of endometrial hyperplasia after one year of treatment, three of which were diagnosed upon continuously combined E2/NETA patches: 50/140 (1/123 cases = incidence 0.8%) [78], 50/250 (1/98 cases = incidence 1%) [78], 50/400 (1/89 cases = incidence 1.1%) [78], 25/125 (1 case = incidence 0.8% [79], 1 case = incidence 0.7% [75]). One case of endometrial hyperplasia (incidence 1.3%) was reported upon treatment with a sequentially combined E2/NETA patch (50/250) [44]. Overall, three endometrial/cervical cancers were reported after one year of treatment with continuously combined E2/NETA patches: 25/125 (one case) [75], 50/170 (two cases) [81]. One 1-year, placebo-controlled RCT assessed endometrial safety in 1741 postmenopausal women using intranasal continuously combined E2/NETA at varying NETA doses (50, 175, 350 mcg/day) [76]. There were four cases of endometrial hyperplasia in the lowest NETA dose group (incidence 1%), but no endometrial cancer an any group.

Levonorgestrel

Two 2-year, placebo-controlled RCTs [36,82] assessed the endometrial safety of oral levonorgestrel (LNG) in combined MHT in 75 [82] resp. 123 [36] postmenopausal women (Supplementary table 6). In both studies, LNG at 75 mcg/day was sequentially combined with standard-dose E2. There were no cases of endometrial hyperplasia or cancer. Five RCTs [42,57,66,83,84] assessed the endometrial safety of intrauterine LNG in continuously combined MHT (Supplementary table 6). All studies were head-to-head comparisons. Sample size ranged from 32 [66] to 190 [57] peri- and/or postmenopausal women. Study duration was one year in all but one RCT (two years) [57]. Endometrial safety was assessed by endometrial biopsy at baseline and study end in all studies. Intrauterine LNG doses ranged from 5 mcg/day [84], 10 mcg/day [42,84], to 20 mcg/day [42,57,66,83]. Estrogen components were either oral or transdermal E2(V) at standard-dose [42,57,66,84], or low-dose [83], respectively. None of the studies reported any cases of endometrial hyperplasia or cancer. In 2011, a systematic review and meta-analysis came to the same conclusion [93]. Two 1-year, head-to-head comparison RCTs [85,86] assessed the endometrial safety of transdermal LNG in combined MHT (Supplementary table 6). Sample sizes were 468 [85] and 855 [86] postmenopausal women, respectively. Transdermal LNG at 10 mcg/day [85], 15 mcg/day [85,86], 20 mcg/day [85], 30 mcg/day [86], or 40 mcg/day [86] was either continuously [86] or sequentially [85] combined to standard-dose [85,86] or high-dose E2 [85], respectively. Only one study reported two cases of endometrial hyperplasia [85]. There was no endometrial cancer.

Dienogest

Only one study [61] assessed the endometrial safety of oral dienogest (DNG) in combined MHT (Supplementary table 7). This was a 1-year, head-to-head comparison RCT in 581 postmenopausal women. Oral standard-dose E2V was continuously combined with DNG at either 2 mg/d or 3 mg/day and compared to standard-dose E2 continuously combined with oral NETA. There were no cases of endometrial hyperplasia or cancer reported.

Gestodene

Overall, two original studies [87,88] assessed the endometrial safety of oral gestodene (GSD) in combined MHT (Supplementary table 7). Both studies were head-to-head comparison RCTs. Each study included 30 postmenopausal women. Study duration was either six months [88], or one year [87]. In the first study [87], standard-dose E2 was sequentially combined with GSD at either 25 mcg/day or 50 mcg/day for 12 days. There were no cases of endometrial hyperplasia or cancer. The second study [88] applied GSD in an extended cycle regimen, after 72 days of either low-dose or standard-dose E2 GSD at 50 mcg/day was applied for 12 days. In 14.8% of women, hyperplasia was found at the end of the estrogen-only phase which disappeared in all cases after the combined estrogen-progestogen phase. There were no cases of endometrial cancer.

Desogestrel

Overall, two 2-year placebo-controlled RCTs [31,36] assessed the endometrial safety of oral desogestrel (DSG) in combined MHT (Supplementary table 7). They included 73 [31], and 123 [36] postmenopausal women, respectively. Oral E2 at 1.5 mg/day was sequentially combined with DSG at 150 mcg/day for 12 days in both studies. Active comparators were combined MHT containing either oral MPA [31,36] or oral LNG [36]. There were no cases of endometrial hyperplasia or cancer reported upon use of oral DSG in combined MHT.

Norgestimate

Only one 1-year head-to-head comparison RCT [68] assessed endometrial safety of oral norgestimate (NGM) in combined MHT in 657 postmenopausal women (Supplementary table 7). Low-dose or standard-dose E2 was sequentially combined with NGM at either 90 mcg/day or 180 mcg/day, respectively. A continuously combined MHT containing standard-dose E2 and oral NETA at 1 mg/day was the active comparator. There were no cases of endometrial hyperplasia or cancer.

Spirolactone derivative

Four studies assessed the endometrial safety of oral drospirenone (DRSP) in combined MHT (Supplementary table 8) [60,83,89,90]. All studies were RCTs, of which three were head-to-head comparisons [60,83,89] and one a placebo-controlled trial [90]. Sample size ranged from 34 [83] to 1063 [89] postmenopausal women. Study duration ranged from 12 weeks [90] to one year [89]. Oral low-dose [60,83,89] resp. ultralow-dose E2 [60,90] was continuously combined with DRSP at varying doses ranging from 0.25 mg [60,90], 0.5 mg [90], 1 mg [89], 2 mg [83,89] to 3 mg [89], respectively. As an active comparator either E2 alone [89,90], or combined MHT using oral NETA [60], or LNG-IUD [83] was used. In all studies, endometrial safety was assessed by endometrial biopsy. Endometrial hyperplasia was reported in 4.0% of women using E2 alone for one year [89]. Only one study reported one case of simple hyperplasia without atypia in a woman receiving E2 at 1 mg/day and DRSP at 2 mg/day for one year. Here, the probability of hyperplasia over a 1-year treatment period was calculated to be 0.007 [89]. Overall, no case of endometrial cancer was reported.

Discussion

Menopausal women with an intact uterus choosing estrogens for menopausal symptom relief require a progestogen for endometrial protection [1,2]. Various progestogens are available worldwide, either in fix combinations or as mono-substances for free combinations with estrogens. For a fix combined MHT to get approval from regulatory authorities like FDA, it is mandatory to prove its endometrial safety for one year by endometrial biopsies [94]. Accordingly, the upper limit of the 95% confidence interval of the incidence of hyperplasia or carcinoma should not exceed 2% after one year, requiring a sample size of 300 patients. For continuously combined MHT, a recent meta-analysis reported a significant reduction of endometrial cancer risk when compared to non-MHT use [95]. However, the authors did not differentiate between MHT regimens and progestogen types.

Thus, to our knowledge, this is the first systematic review addressing the endometrial effect of various progestogens in combined MHT. We only included RCTs that performed endometrial biopsies to

ensure endometrial protection. We found that 1) due to FDA guidance, most studies included postmenopausal women only, although many perimenopausal women also use combined MHT for symptom relief, 2) the number of studies is highest for NETA, followed by MPA, MP and DYD and LNG, 3) most progestogens are only available as oral formulations (DYD, MPA, CMA, CPA, INN, NOMAC, TMG, DNG, GSD, DSG, NGM, DRSP), while 4) various routes of administration have been studied for MP (oral, vaginal, intramuscular, transdermal), NETA (oral, transdermal, intranasal), and LNG (oral, transdermal, intrauterine), respectively. Furthermore, 5) the most frequently studied progestogens (oral MP, DYD, MPA, oral and transdermal NETA, transdermal LNG) have been assessed in continuously as well as in sequentially combined MHT regimens, while other progestogens were only assessed in continuously combined (intranasal NETA, intrauterine LNG, DNG, DRSP), or sequentially combined MHT regimens (CMA, INN, NOMAC, oral LNG, GSD, DSG), respectively. Importantly, 6) FDA endometrial safety criteria (1-year RCT including 300 postmenopausal women with endometrial biopsies for endometrial histology assessment) were only fulfilled by some progestogen formulations (sequential/continuous oral MP, sequential/continuous DYD, sequential/continuous MPA, sequential CMA, sequential/continuous TMG, sequential/continuous oral/transdermal NETA, sequential/continuous transdermal LNG, continuous DNG, sequential NGM, continuous DRSP). Finally, 7) apart from ELITE (vaginal MP at 45 mg/day for 10 days/month), all included studies demonstrated endometrial protection for the progestogen dose and time period examined, where 8) MPA in a continuously combined MHT regimen even has been shown to have a sustainably endometrial protective effect even eight years postintervention. However, 9) study quality varied which should be taken into account when choosing a combined MHT, especially if off-label-use is chosen.

One strength of our review is the broad spectrum of progestogens analyzed. The results may explain why certain progestogen formulations have been approved in combined MHT while others, although frequently used off-label, are not. Yet, there are some limitations as we restricted our literature search to RCTs that performed endometrial biopsies to rule out hyperplasia and cancer. Thus, we might have missed studies, e.g., reporting endometrial cancer incidences as part of their serious adverse event reporting. Furthermore, RCTs that intend approval by regulatory authorities might include healthier participants than so-called real-world-evidence studies. Also, our focus clearly was on endometrium protection thus ignoring other aspects when choosing a MHT preparation. Still, from a practical point of view, one of the biggest challenges today is the fact, that many combined MHT but also progestogen mono-substances have “disappeared” from the market. Thus, choosing the optimal MHT or progestogen for an individual woman is not always possible.

Practice points

Micronized progesterone (MP)

- Depending on the estrogen dose in continuously combined MHT, oral MP at 50–200 mg/day has been shown to be protective for the endometrium for up to one year.
- Depending on the estrogen dose in sequentially combined MHT, oral MP at 100–400 mg/day has been shown to be protective for the endometrium for up to three years.
- Vaginal MP at 45 mg/day has been shown to be not protective for the endometrium if applied in a sequentially combined MHT regimen.
- There is insufficient data to support the use of intramuscular or transdermal MP for endometrial protection in combined MHT.

Progesterone derivatives

- Depending on the estrogen dose in continuously combined MHT, oral DYD at 2.5–20 mg/day has been shown to be protective for the endometrium for up to one year.
- Depending on the estrogen dose in sequentially combined MHT, oral DYD at 2.5–20 mg/day has been shown to be protective for the endometrium for up to two years.

- Oral MPA effectively protects the endometrium in combined MHT for up to nine years of MHT use.
- There is insufficient data to support the use of extended-cycle MHT containing oral MPA.
- In comparison to DYD and MPA, the number of studies assessing endometrial safety is lower for CMA, CPA, INN, NOMAC and TMG.

19-nortestosterone derivatives

- NETA is the most frequently studied progestogen in combined MHT.
- Oral NETA effectively protects the endometrium in combined MHT for up to two years of MHT use.
- Transdermal NETA effectively protects the endometrium in combined MHT for up to one year of MHT use.
- There is insufficient data to support the use of extended-cycle MHT containing oral NETA.

- Intrauterine LNG provides endometrial protection in combined MHT for up to 2 years.
- In comparison to NETA and intrauterine LNG, the number of studies assessing endometrial safety is lower for oral/transdermal LNG, DNG, GSD, DSG, and NGM.

Spirolactone derivative

- For low-dose continuously combined MHT containing E2/DRSP endometrial safety has been proven in postmenopausal women for up to one year.

Research agenda

- So far, there is no meta-analysis on the impact of different combined MHT regimens on the endometrium.
- Real-world-evidence studies investigating fix and free combinations of various progestogens with estrogens might give insight in real-life risk of endometrial hyperplasia and cancer in various at-risk populations.
- So far, the focus has been on postmenopausal women. As many perimenopausal women present with abnormal uterine bleeding, the endometrial “strength” of various progestogens would be of interest for comparison.

Summary

Menopausal women with an intact uterus choosing estrogens for menopausal symptom relief require a progestogen for endometrial protection. The aim of this systematic review was to evaluate the risks of endometrial hyperplasia resp. malignancy with different progestogens used in combined MHT depending on their doses, regimens and duration of treatment. Overall, 84 RCTs fulfilled the inclusion and exclusion criteria. We found that 1) most studies were done with NETA, followed by MPA, MP and DYD and LNG, 2) most progestogens were only available as oral formulations (DYD, MPA, CMA, CPA, INN, NOMAC, TMG, DNG, GSD, DSG, NGM, DRSP), 3) the most frequently studied progestogens (oral MP, DYD, MPA, oral and transdermal NETA, transdermal LNG) were assessed in continuously as well as in sequentially combined MHT regimens, 4) FDA endometrial safety criteria were only fulfilled for some progestogen formulations, 5) most studies demonstrated endometrial protection for the progestogen dose and time period examined. However, 6) study quality varied which should be taken into account when choosing a combined MHT, especially if off-label-use is chosen.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.beem.2023.101815.

References

*[1] The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause 2022;29(7):767–94. https://doi.org/10.1097/GME.0000000000002028. PMID: 35797481.
*[2] Lambrinoudaki I, et al. Menopause, wellbeing and health: a care pathway from the European Menopause and Andropause Society. Maturitas 2022;163:1–14.
*[3] Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. Climacteric 2005;8(Suppl 1):3–63.
[4] Borissov N, et al. Reducing systematic review burden using Deduklick: a novel, automated, reliable, and explainable de-duplication algorithm to foster medical research. Syst Rev 2022;11(1):172.
[5] National Heart, L., and Blood Institute. Study Quality Assessment Tools. 2013 [cited 2023].
*[6] Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA 1996;275(5):370–5.
[7] Lobo RA, et al. A 17β-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial. Obstet Gynecol 2018;132(1):161–70.
*[8] Mirkin S, et al. Endometrial safety and bleeding profile of a 17β-estradiol/progesterone oral softgel capsule (TX-001HR). Menopause 2020;27(4):410–7.
[9] Darj E, et al. Clinical and endometrial effects of oestradiol and progesterone in post-menopausal women. Maturitas 1991;13(2):109–15.
[10] Holst J, Cajander S, von Schoultz B. Endometrial response in post-menopausal women during treatment with percutaneous 17 beta-oestradiol opposed by oral progesterone. Maturitas 1986;8(3):201–7.
[11] Jondet M, et al. Comparative endometrial histology in postmenopausal women with sequential hormone replacement therapy of estradiol and, either chlormadinone acetate or micronized progesterone. Maturitas 2002;41(2):115–21.
[12] Moyer DL, et al. Micronized progesterone regulation of the endometrial glandular cycling pool. Int J Gynecol Pathol 2001;20(4):374–9.
[13] Pelissier C, et al. Chlormadinone acetate versus micronized progesterone in the sequential combined hormone replacement therapy of the menopause. Maturitas 2001;40(1):85–94.
[14] Cortés-Bonilla M, et al. Treatment of menopausal symptoms with three low-dose continuous sequential 17β-estradiol/progesterone parenteral monthly formulations using novel non-polymeric microsphere technology. Gynecol Endocrinol 2015;31(7):552–9.
*[15] Sriprasert I, et al. Use of oral estradiol plus vaginal progesterone in healthy postmenopausal women. Maturitas 2021;154:13–9.
[16] Leonetti HB, Wilson KJ, Anasti JN. Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium. Fertil Steril 2003;79(1):221–2.
[17] Leonetti HB, et al. Transdermal progesterone cream as an alternative progestin in hormone therapy. Alter Ther Health Med 2005;11(6):36–8.
[18] Bergeron C, Ferenczy A. Endometrial safety of continuous combined hormone replacement therapy with 17beta-oestradiol (1 or 2 mg) and dydrogesterone. Maturitas 2001;37(3):191–9.
[19] Quereux C, et al. Continuous combined hormone replacement therapy with 1 mg 17beta-oestradiol and 5 mg dydrogesterone (Femoston-conti): endometrial safety and bleeding profile. Maturitas 2006;53(3):299–305.
[20] Burch DJ, et al. A dose-ranging study of the use of cyclical dydrogesterone with continuous 17 beta oestradiol. Br J Obstet Gynaecol 1995;102(3):243–8.
[21] Chang TC, et al. 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(2):172–8.

[22] Ferenczy A, et al. 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(1):26–35.
[23] Gelfand MM, et al. Conjugated estrogens combined with sequential dydrogesterone or medroxyprogesterone acetate in postmenopausal women: effects on lipoproteins, glucose tolerance, endometrial histology, and bleeding. Menopause 1997;4(1):10–8.
[24] Hänggi W, et al. Comparison of transvaginal ultrasonography and endometrial biopsy in endometrial surveillance in postmenopausal HRT users. Maturitas 1997;27(2):133–43.
[25] Rees M, et al. A first study to compare two dosages of dydrogesterone in opposing the 50 mg oestradiol implant. Maturitas 1991;14(1):9–15.
[26] Siddle NC, et al. Endometrial, physical and psychological effects of postmenopausal oestrogen therapy with added dydrogesterone. Br J Obstet Gynaecol 1990;97(12):1101–7.
[27] van de Weijer PH, et al. Bleeding patterns and endometrial histology during administration of low-dose estradiol sequentially combined with dydrogesterone. Climacteric 1999;2(2):101–9.
*[28] Anderson GL, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 2003;290(13):1739–48.
[29] Bewtra C, Kable WT, Gallagher JC. Endometrial histology and bleeding patterns in menopausal women treated with estrogen and continuous or cyclic progestin. J Reprod Med 1988;33(2):205–8.
[30] Bruhat M, et al. Effective bleeding control and symptom relief by lower dose regimens of continuous combined hormone replacement therapy: a randomized comparative dose-ranging study. Maturitas 2001;40(3):259–71.
[31] Byrjalsen I, et al. Sequential estrogen and progestogen therapy: assessment of progestational effects on the postmenopausal endometrium. Obstet Gynecol 1992;79(4):523–8.
*[32] Chlebowski RT, et al. Continuous combined estrogen plus progestin and endometrial cancer: the Women's Health Initiative Randomized Trial. J Natl Cancer Inst 2016;108(3).
[33] Heikkinen J, Vaheri R, Timonen U. Long-term safety and tolerability of continuous-combined hormone therapy in postmenopausal women: results from a seven-year randomised comparison of low and standard doses. J Br Menopause Soc 2004;10(3):95–102.
*[34] Heikkinen J, Vaheri R, Timonen U. A 10-year follow-up of postmenopausal women on long-term continuous combined hormone replacement therapy: Update of safety and quality-of-life findings. J Br Menopause Soc 2006;12(3):**115**–25.
[35] Johnson JV, et al. Postmenopausal uterine bleeding profiles with two forms of continuous combined hormone replacement therapy. Menopause 2002;9(1):16–22.
[36] Marslew U, et al. Bleeding pattern and climacteric symptoms during different sequential combined HRT regimens in current use. Maturitas 1994;19(3):225–37.
[37] Mattsson LA, et al. A low-dose start in hormone replacement therapy provides a beneficial bleeding profile and few side-effects: randomized comparison with a conventional-dose regimen. Climacteric 2004;7(1):59–69.
[38] Pansini F, et al. Sequential addition of low dose of medrogestone or medroxyprogesterone acetate to transdermal estradiol: a pilot study on their influence on the endometrium. Eur J Obstet Gynecol Reprod Biol 1996;68(1–2):137–41.
[39] Pickar JH, et al. Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate: two-year substudy results. Fertil Steril 2003;80(5):1234–40.
[40] Pinto AB, et al. Effects of trimonthly progestin administration on the endometrium in elderly postmenopausal women who receive hormone replacement therapy: a pilot study. Am J Obstet Gynecol 2003;189(1):11–5.
[41] Prough SG, et al. Continuous estrogen/progestin therapy in menopause. Am J Obstet Gynecol 1987;157(6):1449–53.
[42] Raudaskoski T, 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(2):136–44.
[43] Rees MC, et al. Endometrial safety and tolerability of triphasic sequential hormone replacement estradiol valerate/medroxyprogesterone acetate therapy regimen. Climacteric 2004;7(1):23–32.
[44] Ross AH, et al. Comparison of transdermal and oral sequential gestagen in combination with transdermal estradiol: effects on bleeding patterns and endometrial histology. Obstet Gynecol 1993;82(5):773–9.
[45] Rossouw JE, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288(3):321–33.
[46] Weinstein L, Bewtra C, Gallagher JC. Evaluation of a continuous combined low-dose regimen of estrogen-progestin for treatment of the menopausal patient. Am J Obstet Gynecol 1990;162(6):1534–9.
[47] Williams SR, et al. A study of combined continuous ethinyl estradiol and norethindrone acetate for postmenopausal hormone replacement. Am J Obstet Gynecol 1990;162(2):438–46.
[48] Williams DB, et al. Assessment of less than monthly progestin therapy in postmenopausal women given estrogen replacement. Obstet Gynecol 1994;84(5):787–93.
[49] Woodruff JD, Pickar JH. Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone. The Menopause Study Group. Am J Obstet Gynecol 1994;170(5 Pt 1):1213–23.
[50] Yildirim G, et al. Effects of two different regimens of continuous hormone replacement therapy on endometrial histopathology and postmenopausal uterine bleeding. Arch Gynecol Obstet 2006;273(5):268–73.
[51] Utian WH, Gass ML, Pickar JH. Body mass index does not influence response to treatment, nor does body weight change with lower doses of conjugated estrogens and medroxyprogesterone acetate in early postmenopausal women. Menopause 2004;11(3):306–14.
[52] Koninckx PR, Lauweryns JM, Cornillie FJ. Endometrial effects during hormone replacement therapy with a sequential oestradiol valerate/cyproterone acetate preparation. Maturitas 1993;16(2):97–110.
[53] Fraser DI, et al. The effects of the addition of nomegestrol acetate to post-menopausal oestrogen therapy. Maturitas 1989;11(1):21–34.
[54] Bouchard P, et al. Bleeding profile and endometrial safety of continuous combined regimens 1 mg 17beta-estradiol/trimegestone versus 1 or 2 mg 17beta-estradiol/norethisterone acetate in postmenopausal women. Gynecol Endocrinol 2005;21(3):142–8.

[55] Koninckx PR, Spielmann D. A comparative 2-year study of the effects of sequential regimens of 1 mg 17beta-estradiol and trimegestone with a regimen containing estradiol valerate and norethisterone on the bleeding profile and endometrial safety in postmenopausal women. Gynecol Endocrinol 2005;21(2):82–9.
[56] Meuwissen JH, et al. A 1-year comparison of the efficacy and clinical tolerance in postmenopausal women of two hormone replacement therapies containing estradiol in combination with either norgestrel or trimegestone. Gynecol Endocrinol 2001;15(5):349–58.
[57] Boon J, et al. Continuous intrauterine compared with cyclic oral progestin administration in perimenopausal HRT. Maturitas 2003;46(1):69–77.
[58] Byrjalsen I, Alexandersen P, Christiansen C. Piperazine oestrone sulphate and interrupted norethisterone: effects on the postmenopausal endometrium. BJOG 2000;107(3):347–55.
[59] Fraser DI, et al. The optimal dose of oral norethindrone acetate for addition to transdermal estradiol: a multicenter study. Fertil Steril 1990;53(3):460–8.
[60] Genazzani AR, et al. 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(4):490–8.
[61] Gräser T, et al. 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(2):109–18.
[62] Iatrakis G, et al. Is dosage of hormone replacement therapy related with endometrial polyp formation? Eur J Gynaecol Oncol 2006;27(4):393–4.
[63] Kurman RJ, et al. Norethindrone acetate and estradiol-induced endometrial hyperplasia. Obstet Gynecol 2000;96(3):373–9.
[64] Limpaphayom KK, Bunyavejchevin S. Clinical effects of 17 beta-estradiol and norethisterone acetate in postmenopausal Thai women. J Med Assoc Thai 2000;83(4):407–16.
[65] Obel EB, 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(1):13–21.
[66] Raudaskoski TH, et al. Transdermal estrogen with a levonorgestrel-releasing intrauterine device for climacteric complaints: clinical and endometrial responses. Am J Obstet Gynecol 1995;172(1 Pt 1):114–9.
[67] Rowan JP, et al. Effects of low-dose norethindrone acetate plus ethinyl estradiol (0.5 mg/2.5 microg) in women with postmenopausal symptoms: updated analysis of three randomized, controlled trials. Clin Ther 2006;28(6):921–32.
[68] Rozenberg S, Caubel P, Lim PC. Constant estrogen, intermittent progestogen vs. continuous combined hormone replacement therapy: tolerability and effect on vasomotor symptoms. Int J Gynaecol Obstet 2001;72(3):235–43.
[69] Samsioe G, et al. One-year endometrial safety evaluation of a continuous combined transdermal matrix patch delivering low-dose estradiol-norethisterone acetate in postmenopausal women. Maturitas 2007;57(2):171–81.
[70] Samsioe G, 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(5):368–79.
[71] Sporrong T, et al. Comparison of four continuously administered progestogen plus oestradiol combinations for climacteric complaints. Br J Obstet Gynaecol 1988;95(10):1042–8.
[72] Stadberg E, Mattsson LA, Uvebrant M. 17 beta-estradiol and norethisterone acetate in low doses as continuous combined hormone replacement therapy. Maturitas 1996;23(1):31–9.
[73] Sturdee DW, et al. Ultra-low-dose continuous combined estradiol and norethisterone acetate: improved bleeding profile in postmenopausal women. Climacteric 2008;11(1):63–73.
[74] van der Mooren MJ, et al. Effects of quarterly hormone replacement therapy on climacteric symptoms, endometrial safety, and lipoproteins. Women'S Heal Menopause 1997:247–51.
[75] Mattsson LA, et al. Continuous, combined hormone replacement: randomized comparison of transdermal and oral preparations. Obstet Gynecol 1999;94(1):61–5.
[76] Rozenberg S, et al. Endometrium protection and acceptability of nasally administered continuously combined hormone therapy: a multicentre, multinational, double-blind trial in post-menopausal women evaluating three regimens of 17beta-estradiol and norethisterone when compared with an orally administered 17beta-estradiol norethisterone regimen. Hum Reprod 2009;24(7):1739–47.
[77] Siddle NC, et al. Dose-dependent effects of synthetic progestins on the biochemistry of the estrogenized post-menopausal endometrium. Acta Obstet Gynecol Scand Suppl 1981;106:17–22.
[78] Archer DF, et al. A randomized comparison of continuous combined transdermal delivery of estradiol-norethindrone acetate and estradiol alone for menopause. CombiPatch Study Group. Obstet Gynecol 1999;94(4):498–503.
[79] Brynhildsen J, Hammar M. Low dose transdermal estradiol/norethisterone acetate treatment over 2 years does not cause endometrial proliferation in postmenopausal women. Menopause 2002;9(2):137–44.
[80] 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 Women's Med 1997;42(Suppl 2):388–98.
[81] Ylikorkala O, Rozenberg S. Efficacy and tolerability of fully transdermal hormone replacement in sequential or continuous therapy at two doses of progestogen in postmenopausal women. Maturitas 2000;37(2):83–93.
[82] Byrjalsen I, et al. Serum placental protein 14 (PP14) reflects endometrial status during hormone replacement therapy. Hum Reprod 1992;7(8):1042–7.
[83] Schvartzman L, et al. Effects of hormone therapy on the endometrium in postmenopausal women: a one year randomized trial of low dose oral estradiol in association with a levonorgestrel-releasing intrauterine system or drospirenone. Rev Bras Saude Matern Infant 2013;13(3):259–66.
[84] Wollter-Svensson LO, et al. Intrauterine administration of levonorgestrel 5 and 10 microg/24 h in perimenopausal hormone replacement therapy. A randomized clinical study during one year. Acta Obstet Gynecol Scand 1997;76(5):449–54.
[85] Sturdee DW, van de Weijer P, von Holst T. Endometrial safety of a transdermal sequential estradiol-levonorgestrel combination. Climacteric 2002;5(2):170–7.
[86] 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(3):195–207.

[87] Okon MA, et al. A prospective randomized controlled study comparing two doses of gestodene in cyclic combined HRT preparations on endometrial physiology. Hum Reprod 2001;16(6):1244–50.
[88] Boerrigter PJ, et al. Endometrial response in estrogen replacement therapy quarterly combined with a progestogen. Maturitas 1996;24(1–2):63–71.
[89] Archer DF, et al. Long-term safety of drospirenone-estradiol for hormone therapy: a randomized, double-blind, multicenter trial. Menopause 2005;12(6):716–27.
[90] Archer DF, et al. A randomized, double-blind, placebo-controlled study of the lowest effective dose of drospirenone with 17β-estradiol for moderate to severe vasomotor symptoms in postmenopausal women. Menopause 2014;21(3):227–35.
[91] Birkhauser MH, et al. Updated practical recommendations for hormone replacement therapy in the peri- and post-menopause. Climacteric 2008;11(2):108–23.
[92] 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(4):275–81.
[93] Somboonporn W, et al. Effects of the levonorgestrel-releasing intrauterine system plus estrogen therapy in perimenopausal and postmenopausal women: systematic review and meta-analysis. Menopause 2011;18(10):1060–6.
[94] U.S. Department of Health and Human Services, Fa.D.A., Center for Drug Evaluation und Research (CDER), Guidance for Industry. Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms-recommendations for clinical evaluation. January 2003.
*[95] Sayedali E, Abdel-Rhman R, Yalin S. Combined hormonal replacement therapy and the risk of endometrial cancer in post-menopausal women: a meta-analysis. Indian J Gynecol Oncol 2022;20(41):1–7.