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REVIEW

The impact of micronized progesterone on the endometrium: a systematic review

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ABSTRACT

Postmenopausal women with an intact uterus using estrogen therapy should receive a progestogen for endometrial protection. International guidelines on menopausal hormone therapy (MHT) do not specify on progestogen type, dosage, route of application and duration of safe use. At the same time, the debate on bioidentical hormones including micronized progesterone increases. Based on a systematic literature review on micronized progesterone for endometrial protection, an international expert panel's recommendations on MHT containing micronized progesterone are as follows: (1) oral micronized progesterone provides endometrial protection if applied sequentially for 12–14 days/month at 200 mg/day for up to 5 years; (2) vaginal micronized progesterone may provide endometrial protection if applied sequentially for at least 10 days/month at 4% (45 mg/day) or every other day at 100 mg/day for up to 3–5 years (off-label use); (3) transdermal micronized progesterone does not provide endometrial protection.

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KEYWORDS
Micronized progesterone; endometrium; menopause; combined estrogen progestogen therapy; hormone therapy

Introduction

The steroid hormone progesterone plays a key role in female reproduction[1]. For therapeutic reasons, micronized progesterone (MP) can be used for endometrial protection when estrogens are applied in menopausal women with an intact uterus[2]. However, there is considerable debate about whether and at which dosage MP provides effective endometrial protection if applied orally, vaginally, or transdermally[3]. To discuss various topics on MP, an international expert meeting of gynecological endocrinologists from the German-speaking countries Austria, Germany and Switzerland was held in April 2015 aiming to provide scientifically proven statements on MP treatment in peri- and postmenopausal women, based on a systematic literature search and discussion of the results. Endometrial protection by MP will be the first topic of the planned series.

Material and methods

A systematic literature search was performed using databases (Medline (Pubmed), Biosis (Medpilot) and Cochrane (Cochrane Library)), clinical trial registers (www.clinicaltrialsregister.eu, www.clinicaltrial.gov, http://apps.who.int/trialsearch/), and the experts' own literature collection). Searches were performed using a combination of keywords and Mesh-terms and text words related to "(post-/peri)menopause" or "hormone/estrogen replacement therapy", "progesterone", "endometrial cancer/neoplasm/hyperplasia" or "endometrial biopsy" or "endometrial proliferation/atrophy". Estrogen dosages were classified as high-dose, standard-dose, low-dose and ultra-low-dose by the expert group according to the definition of the International Menopause Society[4]. No time restriction was applied. The selection process involved a pre-selection via title and/or abstracts by two independent reviewers (A.L., B.H.) based on the PICO criteria (Table 1). Discrepancies between the reviewers were discussed and resolved by consensus. Included abstracts were ordered as full articles. The selection process for full articles was performed accordingly. Meta-analyses and systematic reviews were searched for secondary literature. The final eligibility assessment and evaluation of the studies' quality were performed by the expert group (P.S., J.N., L.W.)

Results

Of 1028 hits, 40 studies were selected for the systematic review and expert panel's discussion[5–45].

Oral application of MP

The effect of oral MP on the endometrium has been assessed by transvaginal ultrasound (TVUS)[5,6,10,16,21], endometrial biopsy[10–26] and endometrial cancer incidence[7–9] (Table 2).

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Table 1. Literature search strategy (PICO criteria); status March 2015.

E1	Population/Patient	All (post/perimenopausal) women (natural or surgical menopause) using systemic estrogen replacement therapy (estradiol or conjugated equine estrogen; estriol and estrogen were excluded)
E2	Intervention	Progesterone (natural), exogenously administered on oral, transdermal or vaginal route; duration of study at least 3 months; in humans
E3	Comparison/control	Synthetic progestogens, placebo, no comparison
E4	Outcome	Endometrium hyperplasia or endometrium carcinoma, endometrial biopsies investigating proliferative/antiproliferative effects, endometrial transformation or atrophy
E5	Article type	Clinical studies, observational/epidemiological studies (meta-analyses and systematic reviews were included in order to search for secondary literature)
E6	Language	All English and German abstracts

Endometrial thickness

Endometrial thickness measured by TVUS was assessed in postmenopausal women in one 3-year, placebo-controlled, randomized, controlled trial (RCT) ($n = 167$)[21] and two 1-year RCTs ($n = 100$) with head-to-head comparisons[5,6]. Participants received continuous, transdermal estradiol (E2) (25[21]–50[5,6] µg/day) which was sequentially combined with either different oral progestogens (medroxyprogesterone acetate (MPA), nomegestrol acetate (NOMAC), dydrogesterone (DYD), MP)[6], MP applied orally or vaginally at different dosages (100 or 200 mg/day)[5] or oral MP 100 mg/day for 2 weeks every 6 months (extended cycle)[21]. In those studies with head-to-head comparisons, there were no significant group differences for endometrial thickness at baseline and after 12 cycles[5,6]. When comparing the baseline endometrial thickness with that at study closure, there was either no change (extended cycle regimen at oral MP 100 mg/day[21], sequential regimen at vaginal MP 200 mg/day[5]), or a significant increase[5,6]. Another two small, non-controlled studies using either oral MP 200–300 mg/day for 10 days per month[16] or 100 mg/day for 23 days per month[10] reported no change[10] or an endometrial thickness of less than 2 mm after 1 year[16].

The method of endometrial thickness assessment was described by two authors only[5,6] using the maximal thickness of the endometrium in the longitudinal plane of the uterus.

Endometrial histology

Endometrial biopsies were performed in 17 studies[10–26] of which eight were RCTs[12,13,15,17,18,21,22,24] including two placebo-controlled RCTs[15,21]. Endometrial biopsy procedure was described by all but six authors[12,13,16,20,21,25]. The majority either used a pipelle de Cornier[14,15,18,22,24,26] or Novak's curette[14,15,18,22,26]. Others used a needle aspiration (pistolet method)[23], vabra suction curettage[10,11,15,19] or performed a conventional dilatation and curettage[17,19]. A hysteroscopy was only performed in one study if no tissue was obtained[20]. The sample size ranged from 17[16] to 596[15] women being postmenopausal in all but one study[16]. Treatment duration ranged from 4 months[12,24] to 5 years[20]. Conjugated equine estrogens (CEE) were the most common estrogen component of menopausal hormone therapy (MHT) while others used 17β-estradiol. Estrogen dosage was either high-dose[14,17,19], standard-dose[10–16,18,20,22–26], low-dose[25] or ultra-low-dose[21]. Estrogens were applied either orally or transdermally. MP was examined either at different dosages ranging from 50 mg/day[12], 100 mg/day[10–12,14,19,21,24–26], 200 mg/day[9,13,15–20,22,23], 300 mg/day[14,16,17,19,24] to 400 mg/day[24] or compared to other progestins (intrauterine levonorgestrel (LNG)[23], oral chlormadinone acetate (CMA)[18,22], oral MPA[15,16]). The regimen of combined MHT differed, ranging from continuously combined MHT (28 days per cycle/whole month), intermittently combined MHT (25 days per cycle followed by a 5-day hormone break) to sequentially combined MHT (continuous estrogen therapy combined with a progestogen for 10–14 days per cycle/month). Endometrial biopsies were taken at the end of all trials and also at baseline in all but four studies[14,19–21]. Evaluation of tissue biopsies differed tremendously. Histomorphology was the most common method used to differentiate between proliferative, secretory and atrophic endometrium[10–14,16–20,22–26], and, if applicable, normal, hyperplastic and cancerous endometrium[10,11,15,19–21,24]. Treatment success may be defined as yielding an atrophic, inactive or secretory endometrium whereas treatment failure corresponds to a proliferative endometrium response or hyperplasia[22]. In addition, some investigators assessed histomorphometry[17], mitotic count[14,26], mitotic index[20], DNA synthesis[26], proliferation index (MIB)[24], or used transmission electron microscopy and biochemistry markers[19].

Treatment success by oral MP was reported by 11 studies[10–14,16,18,19,22,24,25]. Seven studies used a continuous[11,12,16] or intermittent[10,14,24,25], and four studies a sequential[13,18,19,22] MHT regimen. Treatment success was achieved by MP 100–400 mg/day if an intermittent MHT regimen was applied[10,12,14,16,24,25]. However, absolute numbers ranged between 3.8% (MP 100 mg/day)[14] and 100% (MP 200 mg/day)[12] for atrophic, and between 0% (MP 200 mg/day)[12] and 64% (MP 400 mg/day)[24] for secretory endometrium, while a proliferative or mildly active endometrium was found in 0% (MP 100–200 mg/day)[12] to 23.1% (MP 100 mg/day)[14]. Accordingly, treatment success was achieved with a sequential MHT regimen if MP 200–300 mg/day was applied[13,18,19,22]. In detail, the endometrium was found to be atrophic in 20.8%[22] to 56% (MP 200 mg/day)[13], secretory in 62.5% (MP 200 mg/day)[18,22] to 83% (MP 300 mg/day)[19] and proliferative in 8.3%[22] to 31%[13] (MP 200 mg/day). In contrast, other studies found an insufficient endometrial transformation if oral MP was applied intermittently or continuously at 100–200 mg/day[23,26] or sequentially at 100–300 mg/day[17,19,20]. The heterogeneity of results and their interpretation by the authors may be attributed to the differences between cohorts, study designs, endometrium evaluation techniques, thresholds for treatment success, and also to the lack of sufficient correlation between histomorphology and endometrial safety. For example, the lack of complete glandular and stromal progestational changes has not been found to be associated with any detectable impairment in antiproliferative effects.

Table 2. Overview of trials investigating menopausal hormone therapy (MHT) containing oral micronized progestin (MP).

					Dosage and application regimen		Endometrium		
Reference	*Study design*	*Sample size*[a]	*Study duration*	*Reproductive stage*[c]	*Progestogen*	*Estrogen*	*Thickness*[b]	*Histology (biopsy)*	*Results*
Writing Group for PEPI[15]	PC-RCT	596/527 (biopsies)	3 years	Post	Oral MPA 10 mg/day days 1–12, oral MPA 2.5 mg/day, oral MP 200 mg/day days 1–12	Oral CEE 0.625 mg/day	No	Yes: baseline and annually without regard to woman's menstrual cycle	Histology in placebo group ($n = 119$): normal $n = 116$, simple hyperplasia $n = 1$, complex hyperplasia $n = 1$, adenocarcinoma $n = 1$; in CEE-only group ($n = 119$): normal $n = 45$, simple hyperplasia $n = 33$, complex hyperplasia $n = 27$, atypia $n = 14$; in CEE + MPA (sequential) group ($n = 118$): normal $n = 112$, simple hyperplasia $n = 4$, complex hyperplasia $n = 2$; in CEE + MPA (continuous) group ($n = 120$): normal $n = 119$, simple hyperplasia $n = 1$; in CEE + MP (sequential) ($n = 120$): normal $n = 114$, simple hyperplasia $n = 5$, atypia $n = 1$; significant difference for CEE vs. placebo, $p < 0.001$)
Harman[9]	PC-RCT	727/464	37.4 ± 16.6 months	Post	Oral MP 200 mg/day on days 1–12 of each month	Oral CEE 0.45 mg/day or transdermal E2 50 μg/day	No	No	Endometrial cancer assessed as adverse events; no significant difference between MHT and placebo
Prestwood[21]	PC-RCT	167/112	3 years	Post	Oral MP 100 mg/day for 2 weeks every 6 months	Oral E2 0.25 mg/day	Yes: baseline and every 6 months	Yes: after 3 years	Endometrial thickness: slight increase, but no significant difference between groups except at year 2; no significant difference in histology, one case of hyperplasia in each group
Jondet[18]	RCT	336/244 (biopsies)	6-month double-blind, then 12-month open-label	Post	Group 1: oral CMA 10 mg/day; group 2: oral MP 200 mg/day on days 10–24	Transdermal E2 1.5 mg/day on days 1–24	No	Yes: baseline 18 months (days 10–24)	Histology at baseline: atrophic in 91.8%, proliferative in 4.1%, secretory in 3.3%; for E2 + CMA at month 18: atrophic in 19.5%, proliferative in 3.7%, secretory in 76.8%; for E2 + MP at month 18: atrophic in 27.1%, proliferative in 8.3%, secretory in 62.5%
Holst[17]	RCT	32/6 for histomorphometry	6 months	Post	Group 1: oral MP 200 mg/day on days 11–21; group 2: oral MP 300 mg/day on days 11–21	Transdermal E2 3 mg/day for 21 days per month	No	Yes: baseline, at 6 months before and at end of MP application	Histology and histomorphometry at baseline: all atrophic; at month 6: no significant changes in areas of glandular cells, glandular nuclei and stromal nuclei with any MP dosage
Moyer[24]	RCT	107 (21 premenopausal controls)/64 (19)	4 25-day cycles (1 cycle CEE only, then RCT)	Post	Group 1: oral MP 100 mg/day; group 2: oral MP 200 mg/day; group 3: oral MP 300 mg/day; group 4: oral MP 400 mg/day for 10 days/25-day cycle	Oral CEE 0.625 mg/day for 25 days	No	Yes: baseline (after CEE only) to after 3 EPT cycles (day 26)	Proliferation index (MIB): significant reduction in MP 200–400 mg/day and luteal phase compared to CEE only; no difference for 100 mg/day; secretory maturation: 0 in CEE-only, 2/22 in MP 100 mg/day, 5/25 in MP 200 mg/day, 10/19 in MP 300 mg/day, 14/22 in MP 400 mg/day, all premenopausal women in luteal phase, 1 simple hyperplasia without atypia in MP 300 mg/day
Dupont[13]	Single-blinded RCT	63; groups 1 and 2 (hysterectomy) $n1 = 16$,	24 weeks	Post	Groups 3 and 4: oral MP 200 mg/day on days 12–25 each month	Groups 1 and 3: transdermal E2 1.5 mg/day; groups 2 and 4: oral CEE	No	Yes: baseline, week 24	Histology baseline–week 24: atrophic in 23/32–18/32, proliferative in 7/32–10/32, mixed in 1/32–3/32 (*cave*: one is missing)

(*continued*)

Table 2. Continued

Reference	Study design	Sample size[a]	Study duration	Reproductive stage[c]	Dosage and application regimen: Progestogen	Dosage and application regimen: Estrogen	Endometrium: Thickness[b]	Endometrium: Histology (biopsy)	Results
		*n*2 = 15; groups 3 and 4 (intact uterus) *n*3 = 16, *n*4 = 16				0.625 mg/day for 25 days each month (dosage adjusted during first 3 cycles according to symptoms)			
Darj[12]	RCT head-to-head comparison	30/26	4 months	Post	Oral MP group 1: 50 mg/day; group 2: 100 mg/day; group 3: 200 mg/day for 25 days each month	Oral E2 2 mg/day for 25 days each month	No	Yes: baseline, month 4	Histology at baseline and month 4 for group 1: atrophic in 80% and 60%, proliferative in 10% and 20%, secretory in 10% and 10% (dropout 10%); for group 2: atrophic in 90% and 60%, proliferative in 10% and 0%, secretory in 0% and 10% (3 dropouts; for group 3: atrophic in 70% and 100%, proliferative in 20% and 0%, secretory in 10% and 0%
Di Carlo[5]	Open-label RCT	100/80	12 cycles	Post	Group A: oral MP 100 mg/day; group B: oral MP 200 mg/day; group C: vaginal MP 100 mg/day; group D: vaginal MP 200 mg/day; sequential regimen (14–25th cycle day/28-day cycle)	Transdermal E2 patch 50 μg/day	Yes: baseline, end of trial (after progestogen withdrawal bleeding)	No	No significant group differences at baseline and after 12 cycles; significant increase of endometrial thickness when comparing endometrial thickness at baseline and after 12 cycles for groups A–C, but below 6 mm in all cases
Di Carlo[6]	Open-label RCT	100/79	12 cycles	Post	Group A: oral MPA 10 mg/day; group B: oral NOMAC 5 mg/day; group C: oral DYD 10 mg/day; group D: oral MP 200 mg/day; sequential regimen (14–25th cycle day/28-day cycle)	Transdermal E2 patch 50 μg/day	Yes: baseline, end of trial (after progestogen withdrawal bleeding)	No	No significant group differences at baseline and after 12 cycles; significant increase of endometrial thickness when comparing endometrial thickness at baseline and after 12 cycles for all groups, but below 6 mm in all cases
Pelissier[22]	RCT	336/265	18 months (6 months double-blind, 12 months open-label)	Post	Group 1: oral CMA 10 mg/day; group 2: oral MP 200 mg/day from day 11 to 24	Transdermal E2 1.5 mg/day from day 1 to 24/cycle	No	Yes: baseline, months 6 and 18	Baseline CMA: insufficient in 13.7%, atrophic in 75.6%, inactive in 4.4%, secretory in 3.8%, proliferative in 1.9%; baseline MP: insufficient in 16.6%, atrophic in 70.7%, inactive in 5.1%, secretory in 1.9%, proliferative in 5.1%; CMA at month 18: atrophic in 15.8%, inactive in 3.7%, secretory in 76.8%, proliferative in 3.7%, treatment success 63.7%, treatment failure 2.4%; MP at month 18: atrophic in 20.8%, inactive in 3.6%, secretory in 62.5%, proliferative in 8.3%, treatment success 35.8%, treatment failure 3.3%
Lane[19]	Non-randomized prospective	50	12 months	Post	Group 1: oral MP 300 mg/day; group 2: oral MP 200 mg/day; group 3:	Oral CEE 1.25 mg/day	No	Yes: at month 3 on day 6	Histology in group 1 (*n* = 12): 83% with varying degrees of secretory change, 17% with non-secretory pattern; in

(*continued*)

Table 2. Continued

Reference	Study design	Sample size[a]	Study duration	Reproductive stage[c]	Dosage and application regimen: Progestogen	Dosage and application regimen: Estrogen	Endometrium: Thickness[b]	Endometrium: Histology (biopsy)	Results
	trial				oral MP 100 mg/day from day 1 to 10 of the calendar month				group 2 ($n = 13$): 69% with early secretory changes mixed with proliferative or non-secretory type glands, 23% with non-secretory pattern; in group 3 ($n = 11$): 36% with varying degrees of secretory change, 27% with non-secretory pattern, 27% with mild to moderate atypical hyperplasia. Additional methods: transmission electron microscopy, biochemistry
Hargrove[16]	Non-randomized prospective trial	17/15	12 months	Peri, $n = 4$; post, $n = 13$	Group 1: oral MP 2–3 × 100 mg/day; group 2: oral MPA 10 mg/day from day 1 to 10 of the calendar month	Group 1: oral E2 2–3 × 0.35 mg/day; group 2: oral CEE 0.625 mg/day	Yes: baseline, 1, 3, 6, 12 months	Yes: baseline, 1, 3, 6, 12 months	Endometrial thickness (only data at study completion provided): CEE + MP <2 mm, CEE + MPA no pathology; Histology (only data at 6 months provided): CEE + MP atrophy, CEE + MPA proliferative or secretory
Foidart[26]	Non-randomized prospective trial	50 post- and 30 premenopausal women/50 post- and 30 premenopausal women	3–6 months	Post and pre	Group 2: oral MP 100 mg/day across 25 days/month	Group 1: estrogen only (oral CEE 0.625 mg/day or transdermal E2 1.5 mg/day for 3 months), followed by 3 months of combined EPT regimen (oral MP 100 mg/day across 25 days/month); group 2: transdermal E2 1.5 mg/day across 25 days/month	No	Yes: baseline, 3rd EPT cycle (cycle days 21–25)	No distinct secretory pattern nor hyperplasia; preferably mild proliferative pattern; mitotic activity and DNA synthesis increased in ET but reduced in EPT group
Suvanto-Luukkonen[23]	Non-randomized prospective trial	30/27	24 months	Post	Group 1: LNG-IUD (20 µg/day); group 2: oral MP 200 mg/day for 25 days per calendar month; group 3: vaginal MP 100–200 mg/day on 25 days per calendar month	Transdermal E2 1.5 mg/day	No	Yes: baseline, 12, 24 months	Histomorphology at baseline: atrophic in 10/14, mild proliferation in 3/14, inactive in 1/14; for LNG at month 24: atrophic in 15/16, partly proliferative in 1/16; for oral MP at month 24: proliferative in 9/10, inactive in 1/10; for vaginal MP at month 24: inactive in 3/3
Gillet[14]	Non-randomized prospective trial	101/91; high-dose $n = 3$, low-dose $n = 98$	6 months	Post	Group 1 (high dose): oral MP 300 mg/day from day 16 to 25; group 2 (low-dose): oral MP 100 mg/day from day 1 to 21or 25	Group 1 (high-dose): transdermal E2 3 mg/day from day 1 to 25 of each calendar month; group 2 (low-dose): transdermal E2 1.5 mg/day from day 1 to 21 per cycle or day 25 of the calendar month (dosage could be	Yes, if biopsy was insufficient	Yes: after 6 months after at least 12 days of MP during that cycle	Mitoses count in glandular epithelial cells; group 1 ($n = 2$): no mitosis or 1 mitosis/1000 cells, group 2 ($n = 78$): insufficient in 3.8%, atrophic in 3.8%, quiescent in 61.5%, mildly active in 23.1%, partially secretory in 7.7%

(*continued*)

Table 2. Continued

Reference	Study design	Sample size[a]	Study duration	Reproductive stage[c]	Dosage and application regimen: Progestogen	Dosage and application regimen: Estrogen	Endometrium: Thickness[b]	Endometrium: Histology (biopsy)	Results
						adapted during the first 3 months according to symptoms)			
Bolaji[10]	Open prospective trial	40/32	12 months	Post	Oral MP 100 mg/day for 23 days of every calendar month	Oral CEE 0.625 mg/day	Yes: baseline, end of trial	Yes: baseline, 6 months, 12 months between days 20 and 23	Endometrial thickness without change; Histology at baseline: atrophic in 74%, proliferative in 15%, secretory in 7%, simple hyperplasia in 2%; after 12 months: atrophic in 73%, proliferative in 17%, secretory in 7%, simple hyperplasia in 3%
Bolaji[11]	Open prospective trial	40/29	12 months	Post	Oral MP 100 mg/day for 23 days of every calendar month	Oral CEE 0.625 mg/day	No	Yes: baseline, 6 months, 12 months between days 20 and 23	Histomorphology at baseline: inadequate in 7%, atrophic in 47%, secretory in 7%, proliferative in 15%, cystic hyperplasia in 2%; at month 12: atrophic in 17%, secretory in 7%, proliferative in 17%, cystic hyperplasia in 3%
Allen[7]	Prospective cohort study	115 474	Mean follow-up 9.0 years	Post	Current MHT user 29%, combined estrogen–-progestogen therapy 74% (sequential regimen 45%, continuous regimen 16%) containing synthetic progestins (91%) or MP (9%)	Estrogens not further specified	No	No	Endometrial cancer. HR (95% CI): current MHT use 1.41 (1.08–1.83), sequential MHT regimen 1.52 (1.00–2.29), continuous MHT regimen 0.24 (0.08–0.77), MP as progestogen constituent 2.42 (1.53–3.83)
Fournier[8]	Prospective cohort study	65 630	Mean follow-up 10.8 years	Post	Percentage of current MHT users is not provided; 40.2% of combined estrogen–progestogen therapy contained oral MP for a mean duration of 4.2 years	E2 92.8%, CEE 2.2%, weak estrogens (estriol, promestriene) 11.1%	No	No	Endometrial cancer. HR (95% CI): any MHT use 1.33 (1.01–1.76), MP as progestogen constituent: ever use 1.80 (1.38–2.34), current use 1.96 (1.41–2.73), use for $\leq$5 years 1.39 (0.99–1.97) and for >5 years 2.66 (1.87–3.77)
Marengo[25]	Prospective controlled trial	112/110	12 months	Post	Oral MP 100 mg/day for 25 days per calendar month	Transdermal E2 1.5 or 0.75 mg/day for 25 days per calendar month	Yes, but only if inadequate tissue ($n = 5$)	Yes: baseline, 2, 6, 12 months	At 12 months: atrophy 81%, sub-atrophy 14.5%, inadequate tissue 4.5% (mean endometrial thickness in those 3 mm)
Moyer[20]	Observational expanded clinical case report	236/153 ($n = 53$ with adequate tissue)	5 years	Post	Oral MP 200 mg/day 14 days/28 days (increase to 300 mg/day and/or shorten to 10–12 days if required)	Transdermal E2 1.5 mg/day on 21 days/28 days (increase to 3 mg and/or 25 days according to symptoms)	No	Yes: after 5 years at day 2–14 of MP treatment (hysteroscopy + biopsy if no tissue was obtained)	Histology: no hyperplasia or carcinoma, in none of the biopsies did the quantity of secretory maturation equal a fully developed glandular and stromal pattern equivalent to late luteal phase. Moderate secretory maturation in 78% of high E2/high MP group (3/300 for 10 days) but only in 8% of low E2/low MP group (1.5/200 for 14 days)

[a], recruited/analyzed; [b], measured by transvaginal ultrasound; [c], post, postmenopause, pre, premenopause; peri, perimenopause

PEPI, Postmenopausal Estrogen/Progestin Interventions Trial; PC-RCT, placebo-controlled, randomized controlled trial; RCT, randomized controlled trial; CEE, conjugated equine estrogen; E2, 17β-estradiol; MPA, medroxyprogesterone acetate; CMA, chlormadinone acetate; NOMAC, nomegestrol acetate; DYD, dydrogesterone; LNG-IUD, levonorgestrel-releasing intrauterine device; EPT, estrogen–progestogen therapy; ET, estrogen therapy; HR, hazard ratio; 95% CI, 95% confidence interval

Thus, the inhibition of endometrial proliferation may be dissociated from secretory maturational changes[20] and therefore a complete secretory maturation may not be required for the prevention of hyperplasia[14]. Jondet and colleagues even stated that the histological classification using proliferative and secretory items does not represent the physiological aspects seen in normal cycles but rather indicates whether the pathologist is able to detect any progestogenic action[18].

That said, it might be more revealing to assess the prevalence of endometrial hyperplasia in endometrium biopsies. Two small ($n = 40–50$)[10,11,19], one short (4 months)[24] and one study using an extended cycle regimen (MP every 6 months)[21] reported one case with (simple) hyperplasia each[21,24], or an 1% increase of the prevalence of simple hyperplasia[10,11], respectively, using a sequentially[19] or quasi continuously combined MHT[7,8] with MP 100 mg/day. In contrast, the study with the longest intervention (5 years) did not find any case of endometrial hyperplasia or carcinoma in women having applied an 17β-estradiol (E2) patch sequentially combined with MP 200 mg/day[20]. However, there were only 53 endometrial biopsies with adequate tissue in 153 women completing the study. Thus, the largest study to date ($n = 596$) is the placebo-controlled RCT Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) with a 3-year intervention phase using a sequentially combined MHT with MP 200 mg/day among others[15]. In this study, all combined MHT regimens were effective in preventing hyperplasia comparable to placebo.

Endometrial cancer incidence

Endometrial cancer incidence in respect to MHT containing oral MP was assessed by two prospective cohort studies, the European Prospective Investigation into Cancer and Nutrition study (EPIC)[7] and the E3N[8], with E3N being the French cohort of EPIC. The sample size ranged from 65 630[8] to 115 474[7] postmenopausal women; the mean follow-up was 9.0[7] and 10.8[8] years, respectively. A self-administered questionnaire containing information on MHT use was sent to participants once at baseline[7] or every 2–3 years[8]. Within the E3N cohort, a woman who successively took different types of MHT simultaneously contributed to each category. The study designs did not include gynecological examinations. Information on the type of estrogen–progestogen therapy (EPT) regimen (sequential or continuous) was available for 61% of EPT users in EPIC[7] and missing in E3N[8]. Data on adherence to medication, prescription and diagnostic bias were not assessed. While E3N only included EPT users with oral MP, EPIC did not differentiate between oral, vaginal and transdermal MP application. MP dosage was not reported in both, EPIC and E3N. Mean duration of EPT use was 2.5 years in EPIC (irrespective of progestogen constituent)[7], and 4.2 years in users of MP-containing EPT in E3N[8]. During follow-up, 601[7] and 301[8] incident endometrial cancers were reported (e.g. self-report, population cancer registries, health insurance records). Tumor histology was reported in EPIC[7] (not in E3N) and tumor stage in E3N[8] (not in EPIC). In current users of MP-containing EPT, there were 26 endometrial cancer cases in EPIC (2231 non-cases) and 54 cases in E3N (number of non-cases not given). Current use of MP-containing EPT was associated with a significantly increased risk of endometrial cancer in both, EPIC (hazard ratio (HR) 2.42; 95% confidence interval (CI) 1.53–3.83)[7] and E3N (HR 1.96; 95% CI 1.41–2.73)[8]. The impact of treatment duration was only analyzed in E3N, showing an increased risk after more than 5 years of use but not below[8]. Endometrial cancer risk was not assessed in respect to tumor histology, specifically to hormone dependency or independency of the tumor. There is only one 4-year RCT, the Kronos Early Estrogen Prevention Study (KEEPS), comparing oral sequential MHT containing MP (200 mg/day) to placebo[9]. The incidence of endometrial cancer was assessed as an adverse event. There was no significant difference in endometrial cancer cases between MHT users ($n = 3$) and placebo ($n = 0$).

Vaginal application of MP

The effect of vaginal MP on the endometrium has been assessed by TVUS[5,27–36], endometrial biopsy[23,27–39] and endometrial cancer incidence[40] (Table 3).

Endometrial thickness

Endometrial thickness measured by TVUS was assessed in 11 studies[5,27–36] of which four were RCTs[5,27,28,34]. In RCTs, vaginal MP was either compared at different dosages[5,28,34] or to intrauterine LNG[27]. The sample size ranged from 20[32,36] to 136[29] postmenopausal women, and treatment duration from 21 days[32] to 3 years[33]. Estrogens were either applied as a vaginal ring[27,28], orally in standard dose[29], or transdermally in standard dose[5,27,29,31,33–36] and low-dose[30]. Vaginal MP was applied as either a capsule or gel at different dosages ranging from 45 mg/day[29,31], 100 mg/day[5,27,30,33,35,36] to 200 mg/day[5,32,35] or as a vaginal ring[28,34]. Application regimens were either sequential (7–12 days/month)[5,27,29], intermittent[29–31,33,35,36] or continuous[28,32,34]. The method of endometrial thickness assessment was described by six authors only[5,27,30,32,33,35]. Endometrial thickness was measured at the maximal thickness of the endometrium in the longitudinal plane of the uterus, specified as double layer in some studies[27,30,35]. In most studies, endometrial thickness remained unchanged with a sequential (45 mg/day[29], 100 mg/day[27], 200 mg/day[5]) or intermittent (100 mg/day[30,33,36,35], 200 mg/day[35]) regimen. In contrast, three studies reported a significant increase of endometrial thickness with a sequential (100 mg/day[5]), intermittent (45 mg/day[31]) or continuous (vaginal MP ring[34]).

Endometrial histology

Endometrial histology was assessed by biopsy in 14 studies[23,27–39] of which five were RCTs[27,28,34,38,39]. In RCTs, vaginal MP was either compared at different dosages[28,34,39] to oral MPA or transdermal norethisterone sacetate (NETA)[38] or to intrauterine LNG[27]. Baseline biopsies were performed in all but four studies[32,33,36,37]. In few studies, endometrial biopsies were only performed if indicated (e.g. suspect TVUS, uterine bleeding)[28–30]. Endometrial biopsy procedure was described by all authors. The majority either used a pipelle de

Cornier[28,30,32,34] or performed a hysteroscopy-guided targeted biopsy[29,33,36,38]. Others used a Novak's curette[31,37], needle aspiration (pistolet method)[23,35], Gynoscan method[27] or vabra endometrial biopsy[39]. The sample size ranged from 9[37] to 136[29] postmenopausal women, and treatment duration from 21 days[32] to 3 years[33]. Systemic estrogens at high[37], standard[23,27,29,31,33–36,38,39] or low[30] dose were applied either orally[29,39], transdermally[23,27,29–31,33–38] or vaginally[27,28]. Vaginal MP was applied as a capsule or as gel at different dosages ranging from 45 mg/day[29,31,39], 90 mg/day[39], 100 mg/day[23,27,30,33,35–38] to 200 mg/day[23,32,35], as intramuscular injection[32] or a vaginal ring[28,34]. Application regimens were either sequential (7–12 days/month)[27,29,37,38], intermittent[23,29–31,33,35,36,39] or continuous[28,34]. Treatment success[22] was reported by the majority of studies, yielding a predominantly atrophic (intermittent MP 45 mg/day[31], sequential or intermittent MP 100 mg/day[30,33,36,27,38], MP vaginal ring[28,34]) or secretory (intermittent MP 45–90 mg/day[39], sequential[37,38] or intermittent MP 100–200 mg/day[23,36] endometrial response. Treatment failure[22] was reported by three studies showing some proliferative endometrial responses (MP vaginal ring[34], sequential or intermittent MP 100–200 mg/day[35,38]). Only one study reported a hyperplastic endometrium in 10% of women after 1 year without remarkable difference between groups (sequential vaginal MP cream 100 mg/day, oral MPA 10 mg/day, or transdermal NETA 0.25 mg/day)[38].

Endometrial cancer incidence

There was only one 5-year RCT, Early versus Late Intervention Trial with Estradiol (ELITE), comparing sequential MHT containing vaginal MP (45 mg/day) to placebo[40]. The incidence of endometrial cancer was assessed as an adverse event. There was no significant difference in endometrial cancer cases between MHT users and placebo (preliminary data presented at World Congress of International Menopause Society, Cancun, 2014).

Transdermal application of MP

Five studies have been identified investigating the impact of transdermal MP on the endometrium[41–45] (Table 4). All but one study[43] were RCTs, some of which had placebo[41] or a progestin[42] as comparator. Sample size ranged from 27[44,45] to 54[43] postmenopausal women, and study duration from 4[41] to 48[43] weeks. Estrogens were applied either orally[41,42] or transdermally[43–45] with the dosage falling either within the high-dose[44,45] or moderate-dose[41–43] category[46]. Transdermal MP cream was applied either sequentially[41,44,45] or continuously[42,43], and the dosage ranged from 16 mg/day to 64 mg/day[44,45]. Transvaginal ultrasound for endometrial thickness assessment was only performed in one study[43] showing a significant increase when combining estrogens with transdermal MP cream. Endometrial biopsy was performed by all studies comparing pre- and post-treatment histology. While two studies indicated an adequate progesterone opposing effect[41,42], the remainder did not[43–45]. There were two cases of complex hyperplasia[43] but no endometrial cancer was found.

Discussion

Current international guidelines on MHT recommend to combine a progestogen when using estrogen therapy in peri- and postmenopausal women with an intact uterus for endometrial protection[2,47–49]. Progestogen addition should be continuous or sequential for at least 12 days per month, as recently again pointed out by the US Endocrine Society. However, long-term endometrial safety of sequential progestogen addition may be reduced since the combination of estrogens with MP (or dydrogesterone) is associated with an increased risk of endometrial cancer if used for more than 5 years[48]. Yet, compliance, dosage and route of application of MP were not exactly known. Internationally, systemic MP is available at different dosages and routes of application. Also, indication and approval by regulatory authorities may differ from country to country. In Europe, systemic MP is available as a capsule (100 mg, 200 mg) for vaginal or oral application or as vaginal gel (8% corresponding to 90 mg).

During the last years, the debate about (compounded) bioidentical hormones has increased tremendously[50–52]. Therefore, the aim of this international expert group was to provide recommendations on the use of estrogens combined with MP in postmenopausal women in respect to endometrial safety.

The European Medicines Agency (EMA) recommends endometrial biopsies at baseline and study closure as the gold-standard method for evaluation for endometrial hyperplasia during MHT[53]. Per definition, a biopsy is evaluable if there is 'endometrial tissue sufficient for diagnosis'. Endometrial biopsies should be classified into the general classes of atrophic, proliferative, secretory, hyperplasia without atypia, hyperplasia with atypia, cancer and others. Biopsies with insufficient tissue for diagnosis may be categorized as 'atrophic endometrium' if the sonographic endometrial thickness is <5 mm. For a new MHT, combination studies of at least 12 months' duration are required. The upper limit of the 95% confidence interval of the incidence of hyperplasia or carcinoma should not exceed 2% after 1 year, requiring a sample size of 300 patients.

For oral MP, there are only three RCTs following EMA's guideline[15,18,22] All studies used sequential (12–14 days/month) MP at 200 mg/day for either 1.5[18,22] or 3[15] years. When comparing sequential CMA (10 mg/day) to sequential MP (200 mg/day), CMA provided a more complete progestogenic transformation[18,22]. However, according to the PEPI trial, sequential MP (200 mg/day) provided adequate endometrial protection for up to 3 years, comparable to sequential or continuous MPA[15]. When further taking into account the results from KEEPS (sequential MP at 200 mg/day for 4 years)[9] and E3N[8], the panel concluded that in postmenopausal women combining estrogens with sequential (12–14 days/month) oral MP at 200 mg/day (EMA approval) for up to 5 years provides sufficient endometrial protection. If oral MP is to be applied continuously, the initial dosage should also be 200 mg/day. This dose may be lowered off-label to 100 mg/day if an (ultra-) low-dose estrogen therapy has been chosen and amenorrhea persists.

Table 3. Overview of trials investigating menopausal hormone therapy (MHT) containing vaginal micronized progestin (MP).

				Dosage and application regimen		*Endometrium*		
Reference	*Study design*	*Sample size*[a]	*Study duration*	*Progestogen*	*Estrogen*	*Thickness*[b]	*Histology (biopsy)*	*Results*
Ben-Chetrit[28]	RCT	29/18	4–6 months	High MP (3.6 g/ring); Low MP (1.8 g/ring)	Vaginal E2 ring (0.36 g/ring)	Yes: baseline, 1, 2, 4, 6 months	Yes: if endometrial thickness >6.5 mm ($n = 6$)	Endometrial thickness increased in 20.7% (7.7–9.5 mm); histology: atrophic in 4/6 samples, secretory in 1/6 samples, polyp in 1/6 samples, no hyperplasia
Ross[39]	RCT	31/24	3 months	Group 1: 45 mg vaginal; group 2: 90 mg vaginal MP every 48 h	CEE oral 0.625 mg/day	No	Yes: baseline, 1 cycle, 3 cycles (each 2nd cycle phase)	Histology after 3 cycles in group 1: atrophic in 2/11, early secretory in 6/11, late secretory in 2/11; in group 2: atrophic in 1/13, early secretory in 9/13, late secretory in 2/13; no hyperplasia or proliferative endometrium
Noe[34]	RCT	44/42	12 weeks	MP vaginal ring: group 1: 0.5 (5 mg/day) or group 2: 1 g (10 mg/day)	Transdermal E2 50 μg/day	Yes: baseline, 12 weeks	Yes: baseline, 12 weeks	Endometrial thickness in group 1: 3.0 > 4.5 mm, group 2: 3.2 > 4.8 mm (significant increase in both groups, no comparison between groups) Histology in group 1: atrophic in 14/21, insufficient in 1/21, proliferative in 6/21; in group 2: atrophic in 15/21, insufficient in 2/21, proliferative in 3/21(non-significant)
Ferrero[38]	RCT	60/60	1 year	Group 1: MPA oral 10 mg/day for 12 days/month; group 2: NETA transdermal 0.25 mg/day for 14 days; group 3: MP vaginal 100 mg/day 12 days/month	E2 transdermal 50 μg/day	No	Yes: baseline, 6, 12 months (always including hysteroscopy)	Histology in MPA group: atrophic in 13/20, proliferative in 4/20, hyperplastic in 1/20, secretory in 2/20; in NETA group: atrophic in 11/20, proliferative in 5/20, hyperplastic in 3/20, secretory in 1/20, simple hyperplasia in 1/20; in MP group: atrophic in 9/20, proliferative in 2/20, hyperplastic in 2/20, secretory in 7/20
Antoniou[27]	RCT	56/56	12 months	Group 1: vaginal MP 100 mg/day for 7 days/month; group 2: LNG-IUD (20 μg/day)	Group 1: vaginal E2 ring for 3 months (2 mg); group 2: transdermal E2 50 μg/day	Baseline, 1 year	Baseline, 1 year	Endometrial thickness: group 1 2.9 mm >2.6 mm, group 2 3.0 mm >2.8 mm Histology: group 1: atrophic in 27/28 samples, insufficient in 1/28 samples; group 2: atrophic in 20/28 samples, insufficient in 1/28 samples, no proliferation
Cicinelli[37]	Prospective cohort trial	9	4 weeks	Vaginal MP 100 mg/day for 10 days/month	Transdermal E2 100 μg/day	No	After 4 weeks	Secretory endometrium (all samples)
Di Carlo[5]	Open-label RCT	100/80	12 menstrual cycles	Group A: oral MP 100 mg/day; group B: oral MP 200 mg/day; group C: vaginal MP 100 mg/day; group D: vaginal MP 200 mg/day; sequential regimen (14–25th cycle days/28-day cycle)	Transdermal E2 50 μg/day	Yes: baseline, end of study (after progestogen withdrawal bleeding)	No	Endometrial thickness: no significant group differences at baseline and after 12 menstrual cycles; significant increase of endometrial thickness when comparing baseline with after 12 cycles for groups A–C (but <6 mm in all cases)
de Ziegler[29]	Non-randomized prospective trial	136	6 months	Group 1: MP vaginal 45 mg/day for 10 days/month; group 2: MP vaginal 45 mg 2/week	Estrogens (oral E2 valerate 2 mg/day, oral CEE 0.625 mg/day; transdermal E2 50 μg/day)	Yes: baseline, 6, 18 months	Yes, but only if abnormal uterine bleeding and/or endometrial thickness >10 mm	Endometrial thickness: group 1 5.1 > 4.9 mm; group 2: not given. Histology (*n* not given): no hyperplasia or cancer

(*continued*)

Table 3. Continued

				Dosage and application regimen		Endometrium		
Reference	*Study design*	*Sample size*[a]	*Study duration*	*Progestogen*	*Estrogen*	*Thickness*[b]	*Histology (biopsy)*	*Results*
Fernandez-Murga[30]	Non-randomized prospective trial	64/27	1 year	MP 100 mg 2/week	E2 transdermal 2 μg/day	Yes: baseline, 6, 12 months	Yes, if abnormal bleeding occurred	Endometrial thickness: 2.9 mm >3.5 mm (non-significant). Histology: atrophy in all ($n = 7$)
Cicinelli[31]	Prospective observational trial	35/26	1 year	Vaginal P4 45 mg 2/week	E2 transdermal 50 μg/day	Yes: baseline, 12 months	Yes: baseline, 12 months	Endometrial thickness: 3.6 mm >4.6 mm (significant). Histology: at baseline all atrophy, at 12 months atrophy in 92.3%
Miles[32]	Non-randomized prospective trial	20 postmenopausal, 4 premenopausal women	21 days	Group 1: vaginal P4 200 mg every 6 h, starting on cycle day 15; group 2: intramuscular P4 50 mg 2/day	Increasing E2 dosages for oocyte donation	Yes: cycle day 21	Yes: cycle day 21	Endometrial thickness: 11.4 mm (group 1) and 11.1 mm (group 2). Histology: no difference between groups
Cicinelli[33]	Prospective trial	30/23	3 years	Vaginal P4 100 mg every other day	Transdermal E2 1.5 mg/day	Yes: baseline, every 6 months	Yes: After 3 years	Endometrial thickness: 3.4 mm >2.7 mm (3 years). Histology: atrophy in all cases
Suvanto-Luukkonen[35]	Non-randomized prospective trial	60/51	1 year	Group 1: LNG-IUD; group 2: oral MP 100 mg/day; group 3: MP 100–200 mg/day vaginal for 25 days/month	E2 transdermal 1.5 mg/day	Yes: baseline, 3, 6, 12 months	Yes: baseline, 12 months	Endometrial thickness: group 1: 2.0 > 3.0 mm; group 2: 2.4 > 2.7 mm; group 3: 2.5 > 2.4 mm (non-significant change within groups). Histology: group 1: atrophy in 12/18, inactive in 5/18; group 2: inactive in 4/19, partly proliferative in 5/19, mostly proliferative in 8/19, secretory in 1/19; group 3: inactive in 5/14, partly proliferative in 1/14, mostly proliferative in 7/14, secretory in 1/14
Suvanto-Luukkonen[23]	Non-randomized prospective trial	30/27	24 months	Group 1: LNG-IUD (20 μg/day); group 2: oral MP 200 mg/day for 25 days per calendar month; group 3: vaginal 100–200 mg/day on 25 days per calendar month	Transdermal E2 1.5 mg/day	No	Yes: baseline, 12–24 months	Histomorphology at baseline: atrophic in 10/14, mild proliferation in 3/14, inactive in 1/14; for LNG at month 24: atrophic in 15/16, partly proliferative in 1/16; for oral MP at month 24: proliferative in 9/10, inactive in 1/10; for vaginal MP at month 24: inactive in 3/3
Vilodre[36]	Open, uncontrolled prospective trial	20/20	1 year	MP vaginal 100 mg/day for 21/28 days	E2 1.5 mg/day for 21/28 days	Yes: baseline, 1 year	Yes: baseline, 1 year	Endometrial thickness unchanged. Histology after 12 months: atrophy in 11/20, proliferative or secretory pattern in 9/20

[a], recruited/analyzed; [b], measured by transvaginal ultrasound

RCT, randomized controlled trial; CEE, conjugated equine estrogen; E2, 17β-estradiol; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; P4, progesterone; LNG-IUD, levonorgestrel-releasing intrauterine device

Table 4. Overview of trials investigating menopausal hormone therapy (MHT) containing transdermal micronized progestin (MP).

					Dosage and application regimen		Endometrium		
Reference	*Study design*	*Sample size*[a]	*Study duration*	*Reproductive stage*[c]	*Progestogen*	*Estrogen*	*Thickness*[b]	*Histology (biopsy)*	*Results*
Leonetti[41]	PC-RCT	37/32	28 days	Post	Transdermal MP cream; 2×/day at 0%, 1.5% or 4.0% (based on patient's weight)	Oral CEE 0.625 mg/day	No	Yes: pre and post MP application. Histology: 0, inactive; 1, scantly proliferative; 2, moderately proliferative; 3, proliferative; 4, highly proliferative. Endpoint: EPS by ranking all slides relative to each other	Significant EPS reduction by 1.5% and 4.0% MP cream compared to pre-treatment with estrogens
Wren[44,45]	RCT	27/21	12 weeks	Post	Transdermal MP cream at 16 mg/day ($n = 9$) or 32 mg/day ($n = 8$) or 64 mg/day ($n = 10$) for 14 days/cycle (sequential)	Transdermal E2 patch 100 µg/day	No	Yes: pre and post MP application	At BL, $n = 6$ proliferative; at week 48, $n = 19$ proliferative (results for groups not given)
Leonetti[42]	Unblinded cross-over RCT	33/26	6 months per treatment arm	Post	Transdermal MP cream 40 mg/day (continuous) or oral MPA 2.5 mg/day (continuous)	Oral CEE 0.625 mg/day	No	Yes: pre and post MP/MPA application	Histology in MP cream group: atrophic in 81%, proliferative in 19%; histology in oral MPA group: atrophic in 73%, proliferative in 27%; no hyperplasia
Vashisht[43]	Open-label single arm study	54/41	48 weeks	Post	Transdermal MP cream 40 mg/day (continuous)	Transdermal E2 cream 1 mg/day	Yes: pre and post MHT	Yes: pre and post MHT	Endometrial thickness: significant increase from mean 3.3 mm to mean 5.3 mm; Histology at BL: 100% atrophic or insufficient; histology at week 48: atrophic in 29%, secretory in 8%, proliferative in 26%, complex hyperplasia (± atypia) in 5%

[a], recruited/analyzed; [b], measured by transvaginal ultrasound; [c], post, postmenopause.

PC-RCT, Placebo-controlled, randomized controlled trial; RCT, randomized controlled trial; CEE, conjugated equine estrogen; E2; 17β-estradiol; MPA, medroxyprogesterone acetate; EPS, endometrial proliferation score; BL, baseline

For vaginal MP, no study completely followed EMA's guideline and gained approval as an adjunct to menopausal estrogen therapy. However, six studies investigated vaginal MP for at least 1 year and performed endometrial biopsies at baseline and at study closure[23,27,31,35,36,38]. Vaginal MP (45–200 mg/day) was applied either sequentially (7–12 days/month)[27,38] or intermittently (25 days/month)[23,35,36]. The majority of investigators concluded that sequential vaginal MP (100–200 mg/day) was insufficient to produce an adequate endometrial response[23,35,36,38]. When taking into account long-term studies (3–5 years)[33,40], the use of sequential or intermittent vaginal MP does not seem to increase the risk of endometrial hyperplasia or cancer. However, due to the heterogeneity of studies and lack of sufficient data, the panel concluded that in postmenopausal women combining estrogens with sequential (4% corresponding to 45 mg/day on 10 days per month) or intermittent (100 mg every other day) vaginal MP for up to 3–5 years may be safe (off-label use). However, 4% MP vaginal gel is not available on the European market. Finally, the use of transdermal MP for endometrial protection cannot be recommended in postmenopausal women using estrogen therapy.

It remains difficult to interpret these data as there is a broad variety in study designs in terms of dosage per cycle, route of administration, clinical findings, sample size per protocol and even histological readings. Therefore, oral MP at 200 mg daily for at least 12 days per month is the preferred route, dose and duration for postmenopausal women with an intact uterus when using estrogen therapy for up to 5 years due to the currently available data. This conclusion seems to be applicable also for the vaginal treatment route. However, this procedure remains off-label use.

Conclusion

Postmenopausal women with an intact uterus using estrogen therapy should receive a progestogen for endometrial protection. International guidelines on MHT do not specify on progestogen type, dosage, route of application and duration of safe use. Based on a systematic literature review on MP for endometrial protection, an international expert panel's recommendations on MHT containing MP are as follows: (1) oral MP provides endometrial protection if applied sequentially for 12–14 days/month at 200 mg/day for up to 5 years; (2) vaginal MP may provide endometrial protection if applied sequentially for 10 days/month at 4% (45 mg/day) or every other day at 100 mg/day for up to 3–5 years (off-label use); (3) transdermal MP does not provide endometrial protection.

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