

REVIEW ARTICLE

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Criteria for the choice and monitoring of Menopausal Hormone Therapy

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Abstract

To review the criteria for the selection of estrogens and especially progestogens for optimizing Menopausal Hormone Therapy (MHT). The main criteria are primarily derived from the Women's Health Initiative (WHI)-trial, disclosing the main risks like endometrial cancer, coronary heart disease (CHD), stroke, venous thromboembolism (VTE) and breast cancer. In addition observational studies must be considered for individualizing MHT, because WHI has tested only one preparation and has a lot of problems like early opening of the hormone/placebo-code (i.e., loss of placebo control), in 60% MHT-initiation too late, and in 40% risk factors for cardiovascular diseases and breast cancer. Pharmacological properties should be considered, such as only oral, but not transdermal estradiol increases VTE-risk. The choice of progestogens could be dependent on the different "partial effects" on steroid receptors, e.g., use of anti-androgenic progestogens in metabolic syndrome, Polycystic Ovary Syndrome (PCOS) etc., taking advantage of the anti-mineralocorticoid effect of drospirenone to stabilize blood pressure and reduce the risk of stroke, selection of tibolone for patients with sexual dysfunctions because its androgenic properties etc. Most important for the selection of the progestogen is endometrial efficacy, primary indication for progestogens in MHT. Therefore regular endometrial monitoring is recommended, using sequential or continuous combined regimens; "hormonal curettage" and/or the progestogen challenge test to avoid endometrial hyperproliferation. Levonorgestrel-IUD as progestogen component can reduce progestogen-dependent risks, offering also contraception, but often with longer bleeding problems, in contrast to sequential regimens of MHT, which can be used to treat irregular bleedings. Other main indications are treatment of climacteric complaints and prevention of osteoporosis and possible other preventive options. Regarding contraindications, according to the general rules of "class-labeling", they are the same for every MHT despite there are differences in benefits and risks. Choice of the timing of MHT-initiation is crucial to whether cardiovascular prevention (early start) or (like in WHI) increased risk of CHD and stroke occurs. The increased risk of breast cancer can be reduced using progesterone or its isomer dydrogesterone. Since, however, this risk cannot be excluded with any MHT, recommendations for screening on the possible development of breast cancer are given, on the basis of own recent research. Criteria for the selection of MHT are mainly to reduce possible risks as seen in WHI since for every MHT efficacy is good and essentially the same. Often the best choice is estradiol combined with progesterone or dydrogesterone, but also other progestogens should be considered including LNG-IUD, to optimize and individualize MHT.

Keywords Choice of MHT, WHI-trial, Estrogens, Progestogens, Endometrial monitoring, Risk reduction

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1 Introduction

"Menopausal Hormone Therapy (MHT)" is defined as estrogen/progestogen-therapy in peri- and postmenopausal women for treatment of climacteric and genitourinary symptoms and prevention of certain diseases which are (besides other factors) more or less dependent on the estrogen deficiency like osteoporosis, metabolic syndrome, diabetes mellitus, colon cancer or can reduce the incidence of coronary heart diseases (CHD) (if early started). Most specialized societies like the "International Menopause Society (IMS)" or "North American Menopause Society (NAMS)" (Baber et al. 2016; Pinkerton et al. 2017) and also most other experts in this field have now agreed to the name "MHT" instead of "hormone replacement therapy" (HRT) or "hormone therapy" (HT), although the different terminology depends on different assessments and rationales in terms of the therapeutic area. Indeed estrogen/progestogen-treatment is offered not only during the time of peri- or postmenopause but for example also is urgently needed as "replacement" in the sense of endocrinology (comparable to treating thyroid hypofunction with thyroid hormones) even in young women with primary ovarian insufficiency (POI), for example, after chemotherapy, or after bilateral oophorectomy (surgical menopause), i.e., during a long period in women's life (Panay, 2020). For this reason, the old term 'HRT' is also still in use.

In hysterectomized women all relevant guidelines recommend to use only estrogen (e.g. Santen et al. 2010; Sarri et al. 2015; Baber et al. 2016; Pinkerton et al. 2017), because the addition of progestogen can increase three of the main risks observed in the Women's Health Initiative (WHI) -trial, the most important study using MHT, i.e., breast cancer and stroke and, if combined MHT started longer than 10 years after menopause, also the risk of coronary heart disease (WHI Investigators 2002). Estrogen-only therapy in non-hysterectomized women does strongly increase the risk of endometrial cancer, which can be avoided by adding a progestogen in sufficient dosage and duration. Thus the primary and main indication to use progestogens in MHT is to protect the endometrium. Testing and monitoring according this action by observing the bleeding patterns during the different possible MHT regimens, by vaginal ultrasound and in difficult situations also by procedures like hysteroscopy, is a main issue before and during use of MHT. The main risk derived from the estrogen component is the risk of venous thromboembolism (VTE) which certainly can be reduced by the use of transdermal estradiol (gels, patches, spray) instead of oral estrogen preparations (L'Hermite et al. 2008; Santen et al. 2010; Sarri et al. 2015; Baber et al., 2016). This is widely acknowledged although not proven within randomized clinical trials, an example

of the importance of observational studies to individualize the choice of MHT. Thus the question on the choice of MHT mainly meets the question "how to reduce possible risks", not questions on effectiveness for prevention and treatment.

The following will describe the importance of WHI for the evaluation of possible risks, which, however, needs to be supplemented with the results of observational studies, considering also basic concepts of the pharmacology of estrogens and progestogens. Further main topics of this review are the importance of endometrial efficacy comparing different progestogens and different dosing, the monitoring of endometrial efficacy, the principle of early start to reduce cardiovascular risks (Window of opportunity), the breast cancer risk as main issue for doctors and patients and as "outlook" recommendations for screening on mechanisms for breast cancer development on the basis of own research.

2 WHI as basis for guidelines for the use of MHT

2.1 WHI—primary interventional study

The role of MHT in peri- and postmenopausal patients has come into scrutiny since the results of the the WHI-trial have been published. WHI was performed in two separate trials, in non-hysterectomized women ($n=16608$) using conjugated equine estrogens (CEE) 0.625 mg/day continuously combined with medroxyprogesterone acetate (MPA) 2.5 mg/day (WHI Investigators 2002), and in hysterectomized women ($n=10739$) using CEE-only 0.625 mg/day) (WHI Steering Committee 2004) (study duration 5 and 7 years, respectively).

Primarily until today this is the most important study in the field of MHT, because the design was prospective and randomized, with clinical endpoints performed within a patient sample presenting enough size for robust statistical analyses. The trial also was announced in the first publications as "double-blind". However, this indeed was not true for the combined arm because patients and doctors were aware of the hormone treatment due to uterine bleedings with necessity to open the code in more than 40%. In addition there were a lot of other problems, like use of only one hormonal preparation which frequently is used only in USA; in 60% the population sample was too old for starting MHT and 40% having the most serious risk factors like hypertension, obesity, smoking, metabolic disorders, etc.). Nevertheless the WHI-trial has been the basis of most official recommendations on the use of MHT, because unfortunately no other study with comparable study-design and large sample size by testing clinical endpoints has been performed until today. So the WHI is the basis for the guidelines for example of the IMS (Baber et al. 2016), European Menopause and Andropause Society (EMAS) (Neves-E-Castro et al. 2015),

NAMS (Pinkerton et al. 2017), American Endocrine Society (Santen et al. 2010), National Institute for Health and Care Excellence (NICE) guidance (Sarri et al. 2015), Global consensus of 10 international societies (Villiers et al. 2016), US Preventive Services Task Force (Grossmann et al. 2017), German Menopause Society (Ortmann et al. 2009), and German Gynecological Endocrinological Societies (Mueck et al. 2015). The main results expressed in relative risks (hazard ratios) and excessive absolute risks are summarized in Table 1 (Kenemans 2005). (increase of M.Alzheimer risk not significant)

The combined arm of WHI has been stopped in 2002 due to an increased risk of venous thromboembolism, myocardial infarction, stroke and breast cancer (WHI Investigators 2002). The stop of the E-only arm in 2004 (WHI Steering Committee 2004) was in the view of most experts not reasonable, considering the benefit of reducing hip fractures and tendency of cardiovascular protection observed time-dependent during longer treatment. In addition, in contrast to the WHI-combined arm, in the E-only arm, performed in hysterectomized women, no increase but rather a reduction of the breast cancer risk was found, which was significant for patients with more than 80% adherence to study medication according to a sensitivity analysis which later has been published (Stefanick et al. 2006). This result indicates a negative effect of progestogens concerning breast cancer risk. In addition, with E-only there certainly was no increased risk of CHD in contrast to the combined arm. This is

important, because the primary aim of the study was to test if MHT can be used to prevent CHD. Hot flushes, the leading symptom of climacteric women and most important indication of MHT, was present in WHI only in less than 7% of the women—another problem of the study! Although in absolute numbers these risks, mainly derived from the progestogen component, are low, about 0.1%–0.5%/year, the decision for or against MHT treating an individual patient will be focused on the main risks of MHT, i.e., especially on effects in the cardiovascular system and breast.

2.2 Follow-up evaluations of patients in WHI

A later release of data from the WHI-trial has concluded that among postmenopausal women, hormone therapy with CEE plus MPA for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up up to 18 years (Manson et al. 2017). During the intervention phase, all-cause mortality in the pooled cohort was 4.0% with hormone therapy vs. 4.0% with placebo. Compared with placebo, women randomized to receive CEE + MPA had a hazard ratio (HR) of 0.97 (95% CI 0.82–1.16) and women randomized to receive CEE alone had a HR of 1.04 (95% CI 0.89–1.22). During the post-intervention period, the HR for all-cause mortality was 1.04 (95% CI 0.97–1.10) for CEE + MPA and 0.92 (95% CI 0.85–0.99) for CEE alone.

Table 1 WHI: Benefits and Risk – Hazard Ratio (HR) and absolute ‘Excessive Benefit or Risk’ in both study arms^a

	Combined Estrogen/Progestin Study-Arm				Estrogen-Only Study-Arm			
	Placebo ^b	CEE+MPA ^b	HR (95% CI)	ExcR	Placebo ^b	CEE ^b	HR (95% CI)	ExBorR
Breast Cancer	30	38	1.24 (1.01-1.54)	+4	33	26	0.77 (0.59-1.01)	-3.5
CHD	33	39	1.24 (1.00-1.54)	+3	54	49	0.91 (0.75-1.12)	-2.5
Ischemic Stroke	21	29	1.41 (1.07-1.85)	+4	32	44	1.39 (1.10-1.77)	+6
VTE	16	34	2.11 (1.58-2.82)	+9	21	28	1.33 (0.99-1.79)	+3.5
Dementia ^c	22	45	2.05 (1.21-3.48)	+11.5	25	37	1.49 (0.83-2.66)	+6
Colon Cancer	16	10	0.63 (0.43-0.92)	-3	16	17	1.08 (0.75-1.55)	+0.5
Endometrial Ca.	6.9	5.6	0.81 (0.48-1.36)	-0.7	-	-	-	-
Ovarian Ca.	2.7	4.2	1.58 (0.77-3.24)	+0.8	-	-	-	-
Hip Fracture	16	11	0.67 (0.47-0.96)	-2.5	17	11	0.61 (0.41-0.91)	-3
Fractures total	199	152	0.76 (0.69-0.83)	-23.5	195	139	0.70 (0.63-0.79)	-28
All Mortality	53	52	0.98 (0.82-1.18)	-0.5	78	81	1.04 (0.88-1.22)	+1.5

ExBorR excessive benefit (- number) or risk (+ number) /1000 women per 5 years, CEE Conjugated Equine Estrogens 0.625 mg/day, MPA Medroxyprogesterone acetate 2.5 mg/day, HR Hazard Ratio, CI Confidence Interval, CHD Coronary Heart Disease, VTE Venous Thromboembolism

^a Mean age 63 years, range 50–79 years
^b Number of patients per 10,000 women per year
^c Subgroup age > 65 years (Mean 70 years), perhaps dementia of mixed (vascular type)

Important is the difference in risks comparing the results in older and younger patients: Comparison of women aged 50–59 years with those aged 70–79 years showed that the risk was significantly lower for the younger age group, as ratios of HRs for all-cause mortality in the pooled cohort were 0.61 (95% CI 0.43–0.87) during the intervention phase and 0.87 (95% CI 0.76–1.00) during the cumulative 18-year follow-up (Manson et al. 2017). The different dependency of benefits and risks on age can be seen already in the primary intervention study comparing the two age groups 50–59 years vs. 70–79 years, as expressed in Table 2 (Barlow 2005).

Based on these results of WHI, it was suggested that the safety concern attributed in the past to MHT need to be reconsidered and to be put in their right perspective. Unfortunately it took, however, about 15 years after the first publication of WHI, that principle investigators of WHI published that the results analyzed from the total WHI-population (without considering subgroups) should not be extrapolated to the benefits and risks of MHT if started early, like in the subgroup between 50–59 years (Manson and Kaunitz 2016). Only in 2016 principle investigators published that they regret the wrong interpretation of WHI for years, leading to a loss of education in this area, so that young doctors do not know how to decide for MHT and for differentiated individual

prescription. One of the main investigators of WHI described the almost unbelievable conditions for the first publication of WHI (Langer 2017), pointing out that the paper was written by the Project Officer, and submitted to the journal JAMA without involvement of all main investigators who were listed as co-authors. These investigators wanted to make changes before publication – but the publisher of JAMA indicated the results together with the first interpretation already was printed and mailed, and that the press and media have been already informed about the premature stop of the WHI. *"The initial paper was written by a small group from the coordinating center and program office and submitted to the journal without informing or consulting the clinical site principal investigators..... The investigators most capable of correcting the critical misinterpretations were actively excluded from the writing and dissemination activities."* (Langer 2017).

Obviously the main difference between E-only therapy (used in hysterectomized women) compared to estrogen/progestogen, i.e., combined MHT, is related to the risk of breast cancer although in the 18-year cumulative follow-up the increase of breast cancer risk in the combined arm was not significant (HR 1.44; 95% CI 0.97–2.15), but clearly different to the significant decrease of breast cancer in the CEE-only arm (HR 0.55; 95% CI 0.33–0.92) (Manson et al. 2017). So the difference in terms of the

Table 2 WHI: Age Dependency of the Benefits and Risks (Number of diseases per 10,000 women per year and excessive benefit or risk, exBorR)

Combined	Age 50–59 years		Age 70–79 years	
Estrogen/Progestogen CEE/MPA				
	CEE + MPA / Placebo	exBorR	CEE + MPA /Placebo	exBorR
Coronary Heart Disease	22/17	+5	78/55	+23
Ischemic Stroke	14/10	+4	61/48	+13
Hip Fracture	1/3	-2	33/48	-15
Fractures total	111/141	-30	224/285	-61
Colon Cancer	4/5	-1	14/28	-14
Breast Cancer	31/26	+5	54/41	+13
Estrogen-only Study-Arm CEE	CEE/ Placebo		CEE/Placebo	
Coronary Heart Disease	14/24	-10	88/84	+4
Ischemic Stroke	16/16	0	71/57	+14
Hip Fracture	4/1	+3	32/52	-20
Venous Thromboembolism	15/13	+2	40/28	+12
Colon Cancer	7/12	-5	32/15	+17
Breast Cancer	21/29	-8	32/34	-2

ExBorR Excessive benefit (- number) or risk (+ number) per 1,000 women per 5 years, CEE Conjugated Equine Estrogens 0.625 mg/day, MPA Medroxyprogesterone acetate 2.5 mg/day

modified according Barlow DH. *Maturitas* 2005; 51: 40–47

risk of breast cancer shown during the interventional phase of WHI persisted during the long-term follow-up of 18 years. In contrast, the increased risk of CHD during combined MHT was no longer seen in the 18-year cumulative follow-up (HR 1.05; 95% CI 0.89–1.23) although a trend of lower risk using E-only can be suggested (HR 0.89; 95% CI 0.75–1.05). These results from the primary intervention studies and Follow-up evaluations have recently been confirmed also in a 20-year follow-up analysis with focus on breast cancer incidence and mortality (Chlebowski et al. 2020).

2.3 Why the decrease of breast cancer risk using E-only therapy?

It remains unclear, if the observed protective estrogenic effect regarding the development of breast cancer in the E-only arm of WHI (WHI Steering Committee 2004) with a significantly lower breast cancer incidence even after more than 20 years of median cumulative follow-up (HR 0.78; 95% CI 0.65–0.93) (Chlebowski et al. 2020) is related to special components of the complex CEE-mixture, as described in chapter 4.1. However, observational studies suggest similar preventive effects. In the open label, randomised controlled Danish Osteoporosis Prevention Study (DOPS) using exclusively estradiol (2 mg/day) the mortality due to breast cancer decreased significantly to about 60% (RR 0.38; 95% CI 0.15–0.99) (Schierbeck et al. 2012). The population of this study was very different compared to WHI, with risk factors like hypertension, smoking and obesity. Moreover, the Danish women were much younger, only recently postmenopausal, in contrast to the WHI population with the start of MHT for two thirds in ages about 65 years.

Comparing these results also are an argument against the "gap-hypothesis" suggesting that later start of MHT having less breast cancer risk compared to early start because according experiment research the development of apoptotic estrogen action would demand a time-"gap" between loss of endogenous estradiol and start of MHT (Jordan 2015). In addition, there are further arguments against this theory (Mueck & Seeger 2015): Other carcinoprotective mechanisms like the production of certain protective metabolites certainly do not need any time-gap, the reduction of breast cancer risk using estrogen-only seems to be an estrogen-group effect, independent of the time of MHT initiation, but dependent on other factors like cell and stromal factors, risk factors like obesity and smoking etc. which can explain that there have been observational studies showing an increase of breast cancer not only with combined MHT but also with E-only therapy (Collaborative Group on Hormonal Factors in breast Cancer 2019). However, there now is the consensus, that the main risk of the development of breast

cancer depends on the progestogen component, increasing primarily estrogen-dependent proliferation and other estrogen-dependent mechanisms of hormone dependent breast cancer development (Ruan & Mueck 2022a).

3 Observational studies needed for individualized choice of MHT

The main problem of the WHI is, that this study cannot reflect practical conditions: Only one MHT preparation was tested, and only one dosage was used which was, as we know today, the two-fold of the dosage that we would use in women with age beyond 65 years – the mean age during the WHI-study. With the exception of USA mostly various other forms of MHT are used, regarding type of hormones, dosage and application form. In the WHI on average the women were too old at start with MHT (60% beyond 60 years), and about 40% of the population were at high risk particularly for breast cancer and cardiovascular diseases. In addition, since about 40% have been obese (BMI > 30 kg/m²), it is questionable if any MHT may have relevant therapeutic or preventive effects because obese women can produce endogenous estradiol from large depots of estrone sulfate. Addition of exogenous estrogens rather may lead to overdosing as for example can be suggested by the fact that an increased risk of breast cancer in the WHI was observed only in obese women. Table 3 demonstrates that about 40% of the WHI-study population primarily were on higher risk for cardiovascular diseases and breast cancer (WHI Investigators 2002; WHI Steering Committee 2004).

Thus, even though we always have to consider the results of WHI, we have to add the results of observational studies to optimize MHT for those women who are not comparable with the population tested in WHI. Indeed most of the patients in our daily practice are

Table 3 WHI: Study population with high risk for cardiovascular diseases and breast cancer

	WHI Study-Arm	
	CEE+MPA	CEE-only
Mean age during the study	67 years	66 years
BMI > 30 kg/m ²	45 %	34 %
Smokers	48 %	50 %
Before or during the study		
Hypertension	48 %	36 %
Further cardiovascular diseases*)	12%	22%

*) Patients after deep vein thrombosis, pulmonary embolism, myocardial infarction, angina pectoris, by-pass surgeries, angioplastic surgeries, dyslipoproteinemia, diabetes mellitus etc

Modified according to the primary original publications

WHI investigators JAMA 2002; 288:321-33; JAMA 2004; 291:1701-12

younger in age, with less risk factors, and especially we would like to find other types of MHT as used in WHI to reduce possible risks observed in WHI. We also have to investigate the biological plausibility for increased breast cancer risk induced by different progestogens, considering the research on proliferation effects of breast tissue in vitro and in vivo, evaluating also possible risk factors and the mechanisms of the development of breast cancer. Regarding cardiovascular risks, according to about 30 observational studies they can be reduced by early initiation of MHT (i.e., peri- or early postmenopausal women instead beyond 60 years like in WHI), taking advantage of the so called "window of opportunity", an early period of time in which arterial plaques have not yet formed. In contrast starting MHT later, existing plaques can be destabilized leading to cardiovascular and cerebrovascular embolism with the consequence of CHD and stroke. In addition, early use of estrogens elicits via the healthy vascular endothelium the benefits of vasodilatation (release of nitric oxide and prostacyclin with increased blood flow, decrease of the cardiac afterload, avoidance of high blood pressure, etc.) and can achieve positive effects in lipids and glucose metabolism, i.e., cardiovascular prevention can be expected (Mendelsohn & Karas 1999; Mikkola & Clarkson 2002; Speroff 2010; Mueck 2012).

In risk patients the use of transdermal instead of oral estrogen can reduce the risk of venous thromboembolism (Scarabin et al. 2003; Canonico et al. 2007; Canonico et al. 2008; Canonico et al. 2010; Renoux et al. 2010a; Simon et al. 2016) and stroke (Renoux et al. 2010b; Canonico et al. 2016). The use of progesterone or dydrogesterone (retro-isomer of progesterone) as progestogen component largely can avoid the increase of breast cancer risk during MHT (Fournier et al. 2008a; Lyytinen et al. 2009; Schneider et al. 2009; Cordina-Duverger et al. 2013; Stute et al. 2018), although the issue of hormone dependent breast cancer risk seems to be very complex, main topic of our recent research, as we already extensively have reviewed regarding different hormone dependent mechanisms elsewhere, including own research (Mueck et al. 2010; Ruan & Mueck 2022a; Ruan & Mueck 2023).

4 Pharmacological properties should be considered for the choice of MHT

4.1 Estrogens

CEE were used in the WHI and are the most frequently used estrogens in USA. CEE are a mixture of more than 10 estrogenic substances extracted from the urine of horses, 30% are not produced in the human body. It is a variable mixture which also contains up to 200 other steroidal substances (including corticoids). CEE have been the first and only estrogens in the 60s up to the 80s (for this reason used in WHI), but from a scientific view, this

mixture should be no longer used, as estradiol is now available orally and transdermally. Less than 5% estradiol is in the CEE-mixture, and it is impossible to monitor the treatment using CEE by any laboratory methods (Lipert et al. 1999; Stanczyk et al. 2013). In addition it seems reasonable from the endocrinological view to use that estrogen whose deficit is responsible for the symptoms and certain diseases, and this is estradiol and not CEE. An extensive critical review on this issue we recently have published elsewhere (Ruan & Mueck 2022b).

Estradiol (E2) is used orally and transdermally as gels, patches and in some countries now also as a spray. In addition in most countries (like also in China) oral estradiol valerate (E2Val) is used which undergoes rapid metabolism to estradiol and valerate during gastro-hepatic passage. Because valerate has no clinical effect, the efficacy of E2Val is the same as using E2, but because of the split up of valerate the equivalent dosages are different, namely 1:1.25 comparing E2 with E2V.

In contrast to oral E2 or CEE the transdermal E2 preparations (Gels, patches, Spray) are not available in fix-estrogen/progestogen-combinations, with the exception of special "combi-patches", which especially because of adhesion problems are only rarely used. For non-hysterectomized women, the MHT must be in "free combination" adding an oral progestogen, to protect the endometrium from estrogenic hyperproliferation which can increase the risk of endometrial cancer. For this often the choice is micronized progesterone or dydrogesterone, because comparing with other (synthetic) progestogens less risk of breast cancer and cardiovascular risks can be expected. The efficacy of transdermal estradiol is the same like with oral estradiol, but the dosage using oral estradiol must be about 50 times higher because of "first pass hepatic metabolism". Since this effect is avoided using estradiol transdermally, all risks with any dependency on hepatic pathophysiology can be reduced. This is true especially for the risk of venous thromboembolism because most clotting factors are produced in the liver (L'Hermite et al. 2008; Mueck 2012; Baber et al., 2016; Genazzani et al. 2021).

All estrogens for topical-vaginal application should be used for local urogenital problem, because they do not have enough systemic efficacy regarding the usual indications of MHT, with the exception of genitourinary syndrome of menopause (GSM), for example stress incontinence. However, using estradiol preparations systemic side effects cannot be excluded because there can be some systemic resorption causing all the risks and side effects of oral estrogens, such as increased risk venous thromboembolism, including uterine bleeding problems and particularly endometrial cancer. Combination with a progestogen is therefore recommended (Sturdee &

Panay 2010; North American Menopause Society 2013; Bruyniks et al. 2017).

It must be added that in the Western world, "estriol" for vaginal use is the main choice for vaginal complaints. By addition of lactobacilli the dosage can be reduced from 1 mg (=1,000 µg) estriol daily to only 30 µg/day (available as a topical combination-product in some European countries) getting still sufficient local efficacy, as observed also in own research (Ruan & Mueck, 2018). Using this ultra-low dosage of vaginal estriol there is almost no systemic resorption, so it can even be used in patients with breast cancer or with increased risk of venous thromboembolism (Mueck et al. 2018). However, also vaginal estriol preparations in dosages of 0.5–1 mg are thought to have no increased risk of systemic estrogen side effects, in contrast to vaginal estradiol and vaginal CEE, which also can induce endometrial proliferation with the risk of uterine bleedings and endometrial hyperplasia. In contrast, therapy with vaginal estriol-preparations in general has no effect on menstrual bleeding patterns. (Rahn et al. 2014; Bruyniks et al. 2017; Palacios et al. 2015).

4.2 Progestogens

Progestogens, from the point of view of MHT, are defined as sex steroids which are capable of secretorically transforming an estrogen-proliferating endometrium and atrophizing it within a continuous daily combination. Since this is the most important progestagenic property, we describe this effect in a separate chapter and in context with monitoring MHT to avoid bleeding problems. Likewise we separately describe the most important risk, increase of breast cancer incidence, which can occur with all synthetic progestogens (=progestins), perhaps only under certain preconditions, whereas with progesterone and its retroisomer dydrogesterone this increase of risk might be decreased, at least up to eight years of treatment. Progestogens are not used as monotherapy in MHT, with rare exceptions, e.g., to transform estrogen-hyperproliferated endometrium in case of bleeding problems and to "bleed off" by provocation of progestogen-deprivation bleeding (so-called "hormonal curettage"). Comparable indications arise in other areas of application, such as in contraception or endometriosis therapy, although other properties of the progestogens are decisive here, such as ovulation inhibition or effects on endometriosis foci or inflammatory processes.

The classification of progestogens is based on their chemical structure into progesterone derivatives (progesterone, retroisomer dydrogesterone, medrogestone and pregnane=17-hydroxyprogesterone derivatives) and nortestosterone derivatives (estrane and gonane). A special derivative of progesterone is dydrogesterone which is

the retroisomer of progesterone. It has like progesterone beneficial effects in the metabolic and vascular system (Seeger & Mueck 2007), but much stronger endometrial efficacy (Mueck et al. 2009; Mueck & Römer 2018). Drospirenone is assigned to a third substance class, the spiro lactones (Schindler et al. 2003). Dienogest is classified as a nortestosterone derivative, although it has a 17- α -cyanomethyl group instead of a 17- α -ethinyl group (Ruan et al. 2012a). It has pharmacological properties like nortestosterone-derivatives (e.g., strong endometrial efficacy), but also like progesterone-derivatives, e.g., good tolerability with respect of glucose- and lipid-metabolism, and no vasoconstrictory effects. Nomegestrol-acetate is a special 19-nor-progesterone-derivative, similar in pharmacology like progesterone, but with much stronger endometrial efficacy (Ruan et al. 2012b).

The pharmacological properties of progestogens often can be described according to their "partial efficacy" induced by specific steroid receptors, although these were primarily determined experimentally in vitro and in animal experiments. However, they also have clinical relevance. Table 4 also takes into account our own experience and data from clinical studies, based on the usual clinically used doses of the progestogens (Schindler et al. 2003; Kuhl 2005; Stanczyk et al. 2013).

For example, in the presence of rather psycho-nervous negative symptoms (depressive moods, lack of drive, lack of concentration, loss of performance and memory, etc.) or in the case of sexual dysfunction (libido disorders, dyspareunia), progestogens with androgenic partial effects can be recommended. Because, however, they are relatively weak with the dosages in available combined fix-preparations for MHT, to get this effect they should be dosed higher in a free combination. Alternatively for those indications needing androgenic activities tibolone (a special drug derived from norethisterone) can be recommended (Kenemans & Speroff 2005) because it is metabolized to two progestagenic substances with strong androgenic potency. Furthermore during use of tibolone the sexual-hormone-binding globuline (SHBG) is decreased, with the consequence, that free testosterone is increased which is the endogenous active androgen.

Since in our menopausal clinic in Beijing we often have women with "minus symptoms" or sexual dysfunction, we almost every day use tibolone with great success in about 10% of the approximately 250–300 patients treated daily with MHT. To consider are known risks, such as the risk of stroke particularly when starting in old age (Cummings et al. 2008), although this risk is comparable to that of conventional MHT if used in older women. Often described is an increased risk of breast cancer due to the increased risk in the frequently cited LIBERATE

Table 4 Progestogens: "Partial efficacy" induced by specific steroid receptors*

	A-E	E	A	A-A	GLU	A-M
Chlormadinone acetate	++	-	-	++	+	+
Cyproterone acetate	+	-	-	+++	++	-
Medroxyprogesterone ac		++	-	(+)	-	+
Megestrolacetate	+	-	(+)	(+)	-	-
Medrogestone	+	-	-	-	?-	-
Dydrogesterone		+	-	-	-	?
Norethisterone	++	+	+	-	-	-
Tibolon-Metabolites	+	+	++	-	-	-
Levonorgestrel	+	-	++	-	-	-
Norgestimat	+	-	+	-	?	-
Gestoden	+	-	+	-	(+)	+
Desogestrel(Metabolit)	+	-	+	-	(+)	-
Dienogest	+++	-		++	-	-
Nomegestrol acetate	++	-	-	+	-	-
Progesterone	+	-	-	(+)	(+)	(+)
Drospirenone	+	-	-	+	-	++

A-E antiestrogenic (= progestagenic), E estrogen, A androgen, A-A antiandrogen, GLU glucocorticoid, A-M antimineralocorticoid

*) Partial efficacy primarily assessed in experimental research

Modified considering the dosages used in clinical praxis according to Schindler et al. 2003

study (Kenemans et al. 2009). However, in this study tibolone was used in patients after breast cancer whereby an increased risk of breast cancer recurrence was observed, as also would be expected with conventional MHT. The primary risk of breast cancer in postmenopausal women treated with tibolone is not higher either, rather lower compared to conventional MHT; in the randomized, placebo-controlled three-year study LIFT ($n=4,538$) (Cumings et al. 2008) it was even significantly lower (HR 0.32; 95% CI 0.13–0.80). Only MHT with progesterone or its retroisomer dydrogesterone or free combination of estradiol with a LNG-IUD as progestogen may have a lower risk profile, but cannot offer the advantages of androgenic effects (see chapter 5).

On the other side we also often use progestogens with antiandrogenic partial activities, in patients with hyperandrogenism (like with acne, seborrhoea) or for menstrual disorders in young patients with POI or PCOS, in combination with estrogen to protect from long-term consequences of estrogen deficiency (Ruan et al. 2017a; Ruan et al. 2018).

In contrast activation of the glucocorticoid receptor (for example during use of cyproterone acetate) is judged to be disadvantageous in women with diabetic metabolism and due to possible upregulation of thrombin receptor, the latter if women with a disposition to VTE are treated (Kuhl 2005). This partial effect becomes relevant with high dosages of MPA, which as a depot preparation in contraception has shown an increased risk of VTE.

This increase is in contrast to all other progestogens used as mono-substances, which only are involved in the development of VTE if they are combined with ethinyl-estradiol (contraceptives) or with estrogens used in MHT, i.e., estradiol and CEE (Tepper et al. 2016).

The anti-mineralocorticoid partial effect, especially of drospirenone with the specific inhibition of aldosterone receptor, can offer benefits when treating women with a predisposed disorder in the renin–angiotensin–aldosterone system (RAAS). This could be observed in the presence of edema, possibly also in certain forms of premenstrual syndrome and in patients with hypertension with disturbances in this regulating system—a suggested mechanism for the decrease risk of stroke using drospirenone in MHT in contrast to other MHT-preparations (Mueck & Seeger 2004; Oelkers 2005). In rare cases, however, the anti-mineralocorticoid effect, i.e., blocking the aldosterone receptor, can also be disadvantageous, certainly relevant if the kidney function is impaired and in patients with disposition to dehydration (exsiccosis) or risk of hyperkalemia (use of potassium-sparing antihypertensive drugs), because any anti-mineralocorticoid effect involves higher renal elimination of sodium and higher resorption of potassium. In contrast, in women with normal functioning RAAS the aldosterone-inhibiting effect rapidly is counteracted by stimulation of renal renin followed by upregulation of the RAAS so possible negative effects of any anti-mineralocorticoid action do not occur (Krattenmacher 2000; White 2007).

Further progestogen actions may have special clinical importance, like the sedative effect observed only during use of progesterone (if orally administered) due to its special metabolism to allopregnanolone, which can via Gamma-Aminobutyric Acid (GABA) receptors induce hypnotic efficacy (Genazzani et al. 2021). In addition an important criterion for the choice of a progestogen in MHT is tissue neutrality, i.e., no proliferation effects in the breast, neutral in the vasculature and in the metabolic system, maintaining beneficial effects in lipids and glucose metabolism (Mueck & Ruan 2019a). Progesterone, the physiological progestogen, mostly meets those criteria (L'Hermite et al. 2008; Mueck & Ruan 2019b), and also its retroisomer dydrogesterone (Seeger & Mueck 2007), which has stronger endometrial efficacy compared to progesterone (Mueck & Römer 2018). In contrast to various synthetic progestogens these more physiological progestogens do not further increase the estrogen-induced risk of venous thromboembolism (Canonica et al. 2007; Canonico et al. 2010;), have less negative effect regarding risk of stroke (Canonica et al. 2016, Lokkgaard et al. 2017) and they do not antagonize the cardiovascular benefit of estrogens (L'Hermite et al. 2008; Mueck & Ruan 2019b; Genazzani et al. 2021). Of special importance are observational studies suggesting less risk of breast cancer increase during MHT containing progesterone or dydrogesterone, as is described in detail in chapter 8.1.

5 Endometrial monitoring of sequential combined and continuous combined MHT

5.1 Sequential vs. continuous combined MHT—bleedings and dosages

Every type of combined MHT can be used in the two main regimens—sequential-combined (i.e., first estrogen-only followed by estrogen+progestogen phase) or continuous-combined (i.e., daily estrogen plus progestogen). The sequential-combined regimen can be performed with or without a one-week break from hormones, although nowadays the regimens without a break are generally recommended to avoid recurrence of climacteric symptoms during the break and other estrogen-withdrawal symptoms such as menstrual migraine. For sequential-combined MHT, the progestogen phase should be at least 10 days (preferably 12–14 days) per cycle to provide sufficient endometrial protection (Mueck & Römer 2018).

In the available sequential or continuous combined "fix-combinations" the estrogen/progestogen dosages have been assessed in studies performing endometrial biopsies before and after (at least one year) MHT, the precondition of the launch of all MHT-preparations. However, because there is a large individual variability,

for some patients "free combinations" may be necessary using also different progestogens according to results of bleeding patterns and endometrial monitoring. Moreover, for the use of transdermal estradiol (patches, gel, spray) the only choice is free combination with progesterone or a synthetic progestogen, with the exception of "combi-patches" releasing estradiol together with norethisterone acetate or levonorgestrel which, however, only are rarely used because of adhesion problems or/and skin irritations. Not available are combined gels, i.e., releasing a progestogen together with the estradiol.

We have provided Table 5 recommending type and dosage for all available progestogens, dependent on the estradiol dosages within sequential or continuous combined regimens, according to the literature as elsewhere extensively reviewed (Mueck & Römer 2018). In this table, which may be helpful in clinical practice, we also have considered our large own clinical experience in our specialized Menopause Clinic in Beijing (the first official menopause clinic in China), where we also have introduced the "Outpatient Mini-Hysteroscopy" (to our knowledge the first in China) for further endometrial monitoring, especially of risk patients, a procedure which also can help to assess the endometrial potency of the different progestogens.

Sequential MHT is indicated if MHT is started during the premenopause, but can be started and continued also in postmenopausal patients. Regular withdrawal bleeding sometimes even still occurs in late postmenopausal patients, but the bleeding will get shorter and less intensive in time and will finally stop. If patients accept these withdrawal bleeds, there is no need to change to continuous combined regimens. If patients (as most patients) do not like the bleeds, starting continuous combined regimens within the early postmenopausal period is recommended, but not for patients in the perimenopause, because a too high frequency of irregular bleedings must be expected.

With continuous combined regimens, used in postmenopausal patients, it is important to note that no bleeding should occur. Endometrial atrophy should be achieved and maintained during long-term therapy. However, according to our clinical practice and also according to various studies, some spotting and bleeding can occur at the start with these regimens in up to 30% of patients, because some time is needed for the endometrium to become atrophic, especially if MHT is started in early menopause. Because studies with postmenopausal patients who experienced bleeding at the start of continuous combined regimens did not show an increased risk of endometrial cancer, early bleeding during initiation of continuous combined MHT does not require further invasive diagnostic procedures, because all these

Table 5 Progestogens: Practical recommendations for the progestogen dosage for free combination with estradiol, dependent on oral or transdermal estradiol dosage*)

Progestogen	Therapeutic regimen	Daily dosage (according to the dose of oral or transdermal estradiol (E2))		
		Low dose E2*)	Middle dose E2*)	High dose E2*)
Progesterone (oral/preferably vaginal)	Sequential	200 mg	200–300 mg	300–400 mg
	Continuous	100 mg	200 mg	300 mg
Medroxyprogesterone acetate	Sequential	5–10 mg	10–20 mg	20 mg
	Continuous	(2.5–)5 mg	5–10 mg	10 mg
Chlormadinone acetate	Sequential	2–4 mg	4 mg	4–6 mg
	Continuous	(1–)2 mg	2–4 mg	4 mg
Cyproterone acetate	Sequential	1 mg	2 mg	3–5 mg
	Continuous	1 mg	1–2 mg	2 mg
Dydrogesterone	Sequential	10 mg	10–20 mg	20 mg
	Continuous	5(–10) mg	10 mg	20 mg
Norethisterone acetate	Sequential	1 mg	1–2 mg	2 mg
	Continuous	0.5 mg	1 mg	2 mg
Dienogest	Sequential	2 mg	2–4 mg	4 mg
	Continuous	2 mg	2–4 mg	4 mg
Levonorgestrel (intrauterine)	Continuous	20 µg	20 µg	20 µg

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

*) Oral estradiol, low dose: 0.5–1 mg, middle dose: 2 mg, high dose: > 2 mg; CEE (only orally), low dose: 0.3/0.4 mg, middle dose: 0.625 mg, high dose: > 0.625 mg; Transdermal estradiol (gels, patches), low dose: 25–40 µg, middle dose: 50 µg, high dose: > 50 µg; Estradiol spray, low dose: one spray, middle dose: two sprays, high dose: three sprays

For gels, patches, and spray, these are the not the dosages which are within the various available preparations.

For example, gels with (according to the package insert) recommended 1.5 g (= 1,500 µg) daily application or patches containing 3–4 mg do release only about 30–50 µg estradiol into the circulation, same also for the transdermal products. It must be checked in the package insert which dosage will get into the systemic circulation

Table modified according to the literature (Mueck & Römer 2018)

procedures have other risks. However, if bleeding occurs suddenly after longer treatment with continuous combined HRT, further diagnostic procedures are necessary, for example D&C or hysteroscopy to assess endometrial histology and exclude other reasons for the bleeding (polyps, especially endometrial cancer) (Goldstein & Lumsden 2017; Pickar et al. 2020).

A special continuous combined "free combination" is the the use of levonorgestrel-IUD combined with estradiol. This combination is for the use of MHT "off label", but the endometrial efficacy to transform the estrogen-primed proliferated endometrium into secretory phases and thereafter maintaining endometrial atrophy is well known, but only if IUDs releasing 20 µg levonorgestrel/day are used (Suvanto-Luukkonen & Kauppila 1999; Varila et al. 2001; Hampton et al. 2005). It can be the best choice for women who still need contraception and dislike non-hormonal contraceptive alternatives like condoms. This is important because women in perimenopause still can have ovulations, and pregnancies in this age would be of high risk. However, women using those IUDs often have to accept longer bleeding problems until endometrial atrophy will occur, in contrast to sequential

regimens of MHT, which can be used to treat irregular bleedings especially in perimenopausal women.

5.2 Endometrial monitoring: hormonal curettage and progestogen challenge test

We recommend according to our own clinical experience before first start of any MHT to assess the endometrial thickness. In case of irregular bleedings or endometrial thickness > 7 mm (double) a so called "hormonal curettage" can optimize the further treatment for menstrual regulation: This means the use of a synthetic progestogen with strong endometrial efficacy, for example dydrogesterone 10–20 mg or chlormadinone acetate 4–6 mg or dienogest 2 mg, during 10–12–14 days, which often will induce a progestogen withdrawal bleeding (progesterone should not be used because its low endometrial efficacy). After that "hormonal curettage" sequential or continuous combined MHT can be started, best within the third to fifth day of the progestogen-withdrawal bleeding. This method especially also is useful if after start of continuous combined MHT some irregular spottings occur (which is frequent in early postmenopausal women). However, if this is not effective, endometrial histology

is needed (for example by outpatient hysteroscopy) to detect pathological causes for the bleedings like endometrial cancer.

The question remains how to assess the progestagenic endometrial efficacy in the daily routine practice without using invasive methods, to compare the different progestogens for getting the best choice, since endometrial efficacy is the primary indication to combine a progestogen with estrogen replacement. To assess if there could be estrogen-dependent proliferation, even in postmenopausal women, already in the eighties it was recommended to reduce the risk of endometrial cancer during use of MHT by performing a screening using the "progestogen challenge test", i.e., treating women during 10–14 days with progestogen-only to observe if after stop there would be some progestogen-withdrawal bleedings. From the correlation with large epidemiological studies evaluating the risk of endometrial cancer it was concluded that the use of this test can reduce the risk of endometrial cancer in estrogen-treated postmenopausal women and also in pre- and perimenopausal women with increased endogenous estrogens (Gambrell et al. 1980; Gambrell 1987).

From studies correlating the histopathology findings from endometrial biopsies with the results of progestogen-challenge tests was concluded, that this challenge test is a reliable, non-invasive, easy-to-use endometrial screening test, especially for women with increased risk for endometrial cancer (e.g., women with obesity, hypertension, diabetes mellitus, irregular bleedings etc. (Maraghy et al. 1994; Bortoletto et al. 1997). For clinical routine the recommendation was given, that if the test is positive, ultrasonography is required in order to determine who needs a more accurate (invasive) examination of the endometrium. If the test is negative, ultrasonography or assessment of endometrial histology is proposed to be not required, because it could be expected that the endometrium is atrophic (Maraghy et al. 1994; Bortoletto et al. 1997), whereby in the follow-up during MHT no bleedings should occur. Certainly this method will not allow a safe MHT in all women, but since any method with invasive procedures to assess endometrial tissue is involved with its own risks, the assessment of the benefit/risk situation using the progestogen challenge test has been suggested to be adequate and reasonable for the daily routine practice.

With the improvement of ultrasound diagnostic in devices and technique, with newer possibilities of intra-uterine imaging and endometrial tissue sampling (e.g., outpatient hysteroscopy), there have been many controversial discussions about the screening value of this test until today (Schlaff & Coddington 2020). However, according to our experience we estimate the "old" progestogen challenge test (together with ultrasound and

bleeding patterns) still as the best first routine method. Unfortunately there are no studies systematically comparing the different progestogens using this challenge test. Of course we mostly trust on the biopsy studies, however, according to our extensive literature research (Mueck & Römer 2018) we only found very few studies comparing head to head the different progestogens and almost no study comparing different progestogens in the same study-population, considering that bleeding patterns are dependent e.g. on weight (obesity), menopausal status, estradiol level, bleeding patterns before treatment etc., which all can influence the endometrial efficacy of the progestogen when used in MHT. So due to the lack of those comparable studies, for the endometrial monitoring of every individual patient as non-invasive tools the report of bleeding patterns, vaginal ultrasound and progestogen-challenge test remain the best proposal for the choice of the progestogen component regarding its endometrial efficacy.

5.3 Endometrial monitoring during use of micronized progesterone

Using progesterone in MHT, endometrial monitoring particularly is recommended, because progesterone has lower endometrial efficacy compared to all synthetic progestogens. On the other side progesterone is the best choice in terms of cardiovascular safety and elicit the lowest risk for the development of hormone dependent breast cancer. Thus together with transdermal estradiol (which has the lowest risk for venous thrombosis and stroke) the combination often now is described as the "golden standard". However, the primary indication to use any progestogen in MHT is to protect the endometrium. Since dydrogesterone, the retroisomer of progesterone, has mostly the same benefits in the cardiovascular system and breast, but much stronger endometrial efficacy, we in our practice also often use dydrogesterone in free or fix sequential or continuous combined combination with estradiol!

Using oral micronized progesterone-capsules in combination with oral estradiol-tablets an increased risk of endometrial hyperplasia and endometrial carcinoma was seen in two studies (E3N- and EPIC study), however, presumably because the use was too short in time and/or too low of dosage (Stute et al. 2016). More carefully conducted studies with well-reported dosing have not demonstrated this risk, such as the prospective randomized placebo-controlled study PEPI for sequential (PEPI trial Writing Group 1996) and the REPLENISH-trial (Lobo et al. 2018) for continuous combined use, in which REPLENISH tested four oral estradiol/progesterone-capsules (1/100; 0.5/100; 0.5/50; 0.25/50 mg/die). Because these are the first fix combinations for

continuous combined estradiol/progesterone in MHT, in future widely use can be expected due to the higher compliance of patients to fix combinations compared to free combinations, and especially due to the beneficial effects of progesterone in the cardiovascular system and with less risk of breast cancer. However, because those new fix combinations are used orally, as with all oral estrogen preparations a possible risk of venous thrombosis cannot be excluded. Thus the use of transdermal estradiol in free combination with micronized progesterone, with dosages according Table 3, may be still the best choice for risk patients, and in view of many experts still the "golden standard" in MHT (Mueck & Ruan 2019b; Genazzani et al. 2021).

A systematic analysis of 40 studies concluded that the combination of estradiol plus progesterone is endometrially safe if progesterone-capsules are applied vaginally, sequentially with 200 mg/d for 12–14 days or continuously with 100 mg every other day (Stute et al., 2016). The stronger effect when applied vaginally is based on the fact that more progesterone is introduced into the endometrium by a "uterine first-pass effect". In contrast, the endometrial efficacy of transdermal progesterone applications prepared for example as gels have been shown not to be sufficient effective to prevent uterine bleeding problems or hyperplasia, so with these transdermal application forms an increased risk of endometrial cancer cannot be excluded (Ruan & Mueck 2014).

However, for most women, oral use of micronized progesterone capsules provides adequate endometrial protection. But special attention should be paid to irregular bleedings and, if necessary, more frequent vaginal sonography checks should be performed. In case of doubt, the "progestogen challenge test" is recommended and/or the use of high dosages of synthetic progestogens with strong endometrial efficacy (see Table 3) to cause a "hormonal curettage" which can treat preexisting local endometrial hyperproliferation.

6 Indications, preventive additional benefits and contraindications

6.1 Indications and possible preventive benefits

Table 6 summarizes the benefits of optimized MHT, whereby it must be differentiated between 1) officially currently listed indications; 2) proven additional preventive benefits, and 3) presumed additional preventive benefits. Additional preventive benefits with the reduction of the risk of clinically very important diseases only can be expected in case of differentiated and individualized use of MHT and considering other important rules like early start within a "window of opportunity"

Table 6 Indications and preventive additional benefits for HRT

Currently listed indications (Package insert)	Menopausal and urogenital symptoms postmenopausal osteoporosis*) Premature ovarian insufficiency
Curative indications	Bleeding disorders Menopausal symptoms (vasomotor and psychonervous symptoms) Urogenital atrophy Urological symptoms (dysuria, pain) Specific forms of dyslipoproteinemia
Proven preventive indications (Risk reduction)	Urogenital atrophy postmenopausal osteoporosis*) Premature ovarian insufficiency (premature menopause, oophorectomy) Diabetes mellitus Colorectal cancer
Presumed preventive indications (with early onset and differentiated HRT)	Metabolic syndrome Coronary heart disease Alzheimer's disease Various atrophic-degenerative diseases (skin, mucous membranes, connective tissue), rheumatic diseases Certain forms of schizophrenic psychoses Lung cancer?

*) currently limited indication of osteoporosis prevention: in case of intolerance or contraindications to alternatives (if any)

especially for prevention of cardiovascular diseases. There can be expected a benefit for treatment and prevention of climacteric symptoms, GSM, prevention of osteoporotic fractures, prevention and treatment of uterine bleeding problems, and (even it is not in the official labeling) prevention of coronary heart disease (if MHT is early started), further the reduction of the incidence of diabetes mellitus and metabolic syndrome, and as another important possible benefit the prevention of colon cancer (Santen et al. 2010; Sarri et al. 2015; Baber et al. 2016; Genazzani et al. 2021).

Controversial is a possible preventive effect for dementia like Alzheimer's disease because an increase of risk in the WHI was observed, although only in the patients with start of MHT beyond 65 years, on average 70 years (WHIMS=Women's Health Initiative Mental Study). However, increased risk also recently was observed in a large Denish register case/control (n=5,589/55,890) evaluation (Pourhadi 2023), with about 20% increase of risk even in women starting MHT at age of 55 years and younger, in contrast to the results of other (but smaller) observational studies showing a decrease of risk if MHT is early started comparable to the situation regarding coronary heart disease (Henderson 2004). So this issue remains controversial.

6.2 Contraindications and non-hormonal alternatives

According to the official labelling of MHT-products there is a large list of contraindications, summarized in Table 7. It must be stressed, that whereas the efficacy is largely the same for all MHT-preparations (i.e., having the same indications), there are large differences in the risk profil. Despite this fact, the contraindications listed for the MHT are the same according to the rules of health authorities demanding the so called "class-labeling" in the drug leaflets. So in case of MHT the labeling is for the "class estrogens" and "class progestogens" without relevant differences of the various substances, e.g., no difference between transdermal estradiol (gel, patches, spray) or oral estradiol. However, for the clinical practice the differences to know is essential, e.g., if a patient with risk of VTE will get prescribed oral estradiol instead of transdermal estradiol and would suffer from a VTE, this strong prescription mistake would have even forensic consequences.

For patients with contraindications several non-hormonal derived drugs have been recommended, as described elsewhere (e.g., (NAMS, 2015); Ruan et al. 2019; Genazzani et al. 2020), mostly "off label", because climacteric symptoms are not officially listed as indications, like venlafaxine, desvenlafaxine, paroxetine, citalopram, escitalopram, gabapentin, opipramol, clonidine etc. These alternative drugs do not have the strong efficacy for treatment of the typical vasomotor symptoms compared to MHT. Other alternatives are special herbal products with, however, sometimes controversial study

results (Glazier et al. 2001; Krebs et al. 2004). But using special forms of "Tradional Chinese Medicine" in the hands of Chinese experts have shown good efficacy for treatment of menopausal complaints and also for menstrual regulation (Zhang et al. 2020), included the use of acupuncture according to also own experience in thousands of patients as recently reviewed (Qin et al. 2021).

The contraindications primarily take into account the most important risks that have been shown in the WHI-study or that can be explained directly or indirectly with the pharmacological properties of the estrogens and progestins. However, as with other drugs, a large proportion of the contraindications are based on individual reports from the studies, without a causal relationship always being able to be proven. It is often unclear whether the risks can occur only for specific substances or if they are a group effect. Verified differences in the risk profile result from a comparison of oral and transdermal estrogen application, the latter with a reduction in all risks associated with a high estrogen flooding into the liver ("first pass effect"). So in patients with increased risk of venous thrombosis the use estradiol transdermally urgently is recommended (L'Hermite et al. 2008; Santen et al. 2010; Sarri et al. 2015; Baber et al. 2016; Genazzani et al. 2021). It should be mentioned, that according to own research observing five million outpatients in our hospital in Beijing the risk of venous thromboembolism seems to be very rare in China, but high in Western countries, with the consequence that we mostly use oral estradiol preparations (Mueck & Ruan 2015).

Table 7 Contraindications to HRT

Contraindications	
Absolute contraindications**) (listed contraindications)	Unexplained vaginal bleeding, endometrial hyperplasia breast cancer, endometrial cancer (also anamnestic) Acute and anamnestic venous thromboembolism Congenital coagulation disorders Acute myocardial infarction, unstable angina pectoris Acute stroke, unstable hypertension Acute migraine attacks with visual disturbances Known hypersensitivity to active ingredients Pregnancy
Relative contraindications***)	severe liver disease, cholestasis, gallstones Thrombophilia Porphyria, systemic lupus erythematosus severe hypertension, severe heart and kidney disease Severe diabetes with vascular changes Pancreatitis, hyperlipoproteinemia type IV, V Uterus myomatosus, endometriosis Epilepsy, Sydenham's chorea
Controversial contraindications tumours	Asthma, multiple sclerosis, otosclerosis, melanoma, liver

**) Exceptions must be justified in a forensically verifiable manner
***) Treatment possible with individualised differentiated HRT and close monitoring

The most important risks associated with any form of MHT (group effects) concern 1) the risk of endometrial carcinoma, which can be reduced by adequate progestogen addition and largely avoided with regular monitoring; 2) an increased incidence of CHD and stroke, which can be reduced by early initiation of MHT; and 3) an increased risk of breast cancer. Although the breast cancer risk can be reduced by using progesterone or dydrogesterone, it remains the most important risk for doctors and patients, which is why like in our research screening methods are sought to detect this risk early.

7 Cardiovascular prevention or risk depending on the time of MHT initiation

Hundreds of experimental studies in vitro, in vivo and clinically show favorable estrogen effects in the vasculature and metabolic system (primarily lipid and glucose metabolism), which can be antagonized by synthetic progestogens in a dose-dependent manner, while progesterone and its retroisomer dydrogesterone are largely neutral (overview e.g. (Mueck & Ruan 2019b)). At least 30 observational studies have shown prevention of coronary artery disease (CAD), regardless of the type of MHT, if MHT is started early, i.e., optimally within 5, at most 10 years after menopause, while later onset is associated with an increased risk!

"Window of opportunity" means the beginning of MHT as long as arterial plaques have not yet formed, which can be destabilized dependent on estrogen and progestogen use. During this "window" the arterial vessels can respond to the vasoconstrictory progestogen effects by reflective vasodilatation (release of endothelial nitric oxide and prostacyclin), prerequisite for cardiological relief and thus for prevention of CHD (Mueck et al. 2007; Mueck & Seeger 2004; Mikkola et al. 2002). This was clinically shown, for example, in the placebo-controlled "Early vs. Late Intervention Trial with Estradiol (ELITE)" ($n=643$) (Hodis et al. 2016), in which the progression of arteriosclerosis with start of MHT under 6 years compared to over 6 years with was reduced, using estradiol/progesterone combinations.

The DOPS (Schierbeck et al. 2012) showed a 52% significant reduction in heart failure, myocardial infarction, and cardiovascular mortality with initiation of MHT already in the perimenopause or within two years thereafter and prospective follow-up over 10 years, whereby estradiol was combined with norethisterone acetate (NETA), although this gestagen is to be classified as particularly unfavorable in its metabolic and vascular effects. The early start, rather than the choice of the progestogen component, is therefore the decisive approach to avoid a cardiovascular risk under MHT or to maintain the good preventive effect of the estrogen component for CHD.

According to Cochrane Library at least four meta-analyses and one systematic Cochrane reviews have confirmed this (Boardman et al. 2015).

In contrast to CHD, the data for stroke are controversial. A case/control analysis ($n=3,144/12,158$) from a French database showed no risk when MHT was combined with progesterone or progesterone-derivatives, regardless of the time of MHT-initiation, but there was a significant risk increase with NETA-derivatives ((Canonico et al. 2016). In contrast, in an analysis from the Finnish register ($n=489,105$), the mortality from stroke was reduced, but independently of the MHT-type and start of treatment (Mikkola et al. 2015). An analysis from the same register is of great practical importance, according to which sudden discontinuation less than a year after the start of MHT increases the mortality from cardiac and cerebrovascular events (Venetkoski et al. 2018). This the authors attribute to a destabilization of arterial plaques and/or reflectory vasoconstriction due to the sudden withdrawal of MHT, as we feared earlier based on our own experimental data Mueck et al. 2007) confirmed within an EDITORIAL discussing our research (Mikkola et al. 2002). Thus, as important recommendation for the clinical practice, if MHT is to be discontinued, this should not be done suddenly, but the dosage should be gradually reduced and/or the application intervals extended.

8 Trials on breast cancer risk and proposed screening for increased risk

8.1 Breast cancer risk during MHT

As already outlined in the introduction, regarding clinical studies on the risk of breast cancer using estrogen/progestogen therapy the only placebo-controlled trial has been the WHI, showing that addition of MPA to CEE does increase the breast cancer risk, although this increase in the first evaluation of the interventional phase was not significant (HR 1.26; 95% CI 1.00–1.59) (WHI Investigators 2002). It was significant in the second evaluation (HR 1.24; 95% CI 1.01–1.54) (Chlebowski et al. 2003), and the 18-year cumulative follow-up evaluation did show an (non-significant) increase of mortality (HR 1.44; 95% CI 0.97–2.15) (Manson et al. 2017). Striking is the clear difference to CEE-only therapy (WHI Steering Committee 2004), the decrease of risk during interventional phase being almost significant (HR 0.77; 95% CI 0.59–1.01), for patients with documented 80% compliance to study medication significant (HR 0.67; 95% CI 0.47–0.97) (Stefanick et al. 2006), and likewise also the decrease of mortality in the 18-year cumulative follow-up evaluation being clearly significant with a 45% reduce of the incidence (HR 0.55; 95% CI 0.33–0.92) (Manson et al. 2017). The results regarding breast cancer incidence and

mortality all have recently been confirmed in a 20-year follow-up analysis (Chlebowski et al. 2020).

So the possible negative impact of the progestogen component has well demonstrated in clinical studies which is supported by our and other experimental research, as extensively published elsewhere (Mueck et al. 2010; Ruan & Mueck, 2022a). In most studies the synthetic progestogens MPA or NET/NETA have been used. However, observational studies are supporting our and other experimental data, suggesting a lower risk using progesterone or dydrogesterone at least up to eight years compared to synthetic progestogens (Fournier et al. 2008a, Lyytinen et al. 2009; Schneider et al. 2009; Cordina-Duverger et al. 2013; Asi et al. 2016; Stute et al. 2018).

The recent meta-analysis by the "Collaborative Group on Hormonal Factors in Breast Cancer" can only be used to a limited extent on this question, since approximately 40% of the data in this analysis come from the "Million Women Study" (Collaborative Group, 2019), rated as one of the worst observational studies (Stevenson & Farmer 2020). An evaluation of progesterone is not possible from this meta-analysis, since only 50 of the 143,887 women with breast cancer were treated with progesterone. However, this question is of primary importance, since observational studies for the combination with progesterone indicate a lower risk compared to synthetic progestogens (systematic review evaluating 19 studies (Stute et al. 2018), although in the reassessment of the E3N-study according to histological type for lobular carcinomas, a trend towards a higher risk for treatment times longer than five years was seen (Fournier et al. 2008b). This possible increase of risk is biologically plausible, since certain metabolites of progesterone (5- α -Pregnane) can stimulate breast cancer cells if certain cellular conditions for hormone-induced proliferation are present (e.g., membrane-bound receptors which have been also in focus of our research (Ruan & Mueck, 2022a)). However, because other metabolites of progesterone act carcinoprotective (4-Pregnene, inhibiting breast cancer cell proliferation) (Wiebe et al. 2005), there perhaps are different individual risk profiles according to the different ratios of metabolism, which could explain also the different results in clinical studies.

8.2 Outlook: Screening for mechanisms for development of hormone dependent breast cancer

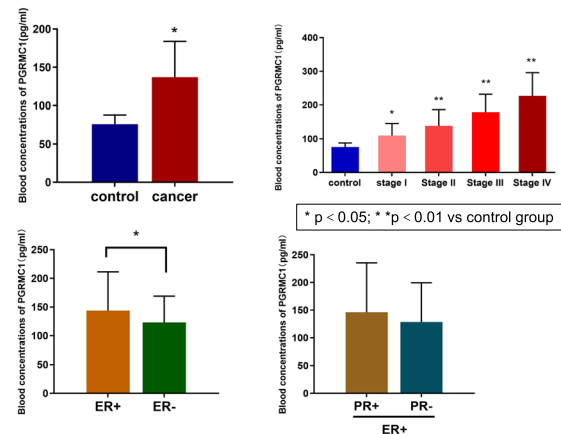
Since an increased risk of breast cancer can obviously not be ruled out with any MHT, even not during use of progesterone or its retroisomer dydrogesterone, our recommendation is to screen on recognized hormone-dependent mechanisms at least for women who are predisposed to a higher risk due to known risk factors

(genetically, obesity, smoking, high alcohol consumption, etc.), potentially with a lower defense against the development of breast cancer. On this issue we have done extensive research over the about last 10 years (overview (Ruan & Mueck 2022a; Ruan & Mueck 2023) Encouraged by Editorials in relevant journals regarding our first publications, with the discussion that our experimental results can explain the increased risk in the WHI study (Stanczyk 2011; Price 2013), we were able to show in more than a dozen published original studies with different breast cancer cell cultures and animal experiments that certain membrane-bound receptors of breast cancer cells can in presence of estradiol increase proliferating progestogen effects whereby, however, progesterone is largely neutral. Recently, we have been able to demonstrate in clinical studies with over 500 breast cancer patients that their expression correlates with known predictive tumor characteristics like tumor size, tumor grading, lymph node status, survival time, i.e., overall indicating a poor prognosis. These receptors, which we first identified directly in breast cancer tissue (Ruan et al. 2017a, b), we were recently able to detect in the blood as well (Ruan et al. 2020), and we could show that screening on these receptors is comparable predictive like other already known tumor markers (Ruan & Mueck 2022a). Figure 1 demonstrates the results of such a study (Ruan et al. 2020).

Another example from our own research is the formation of certain estrogen metabolites described by the WHO as "carcinogenic". In details this research just recently we have reviewed elsewhere (Ruan & Mueck 2023). So-called catecholestrogens can react as intermediates to semiquinone/quinone estrogen-metabolites, which induce deleterious DNA destruction with subsequent point mutations in the replication phases, which can then lead to breast cancer cells (Mueck et al. 2010). However, this only occurs due to defective enzyme systems in connection with excessive and unrestrained oxidative cell stress, e.g., caused by industrial environmental toxins, which was published already years ago in "Science" as summary of a special conference of the American Cancer Society discussing this issue (Service 1998). We were able to show for postmenopausal women that transdermal estrogen application avoids the production of precursors of deleterious quinones/semiquinones.

According to our estimation, the choice of transdermal estradiol, for example, may be clinically relevant for women who smoke or who live in a polluted environment that provides the additional oxidative cellular stress necessary for this mechanism of breast cancer development (Ruan & Mueck 2015). However, a prerequisite for these carcinogenic mechanisms are defective carcinoprotective cell systems, e.g., due to genetic polymorphisms, which

Correlation of PGRMC1 blood concentrations with clinical tumor characteristics



Modified according Ruan X, Cai G, Wei Y. et al. *Menopause* 2020; 27: 183-193

Significant increase of PGRMC1 blood concentrations dependent in breast cancer patients dependant on staging

Fig. 1 Demonstrates the results of such a study

are already being determined in some centers in the sense of a screening. However, they only become clinically relevant as a whole. Therefore considering the large number of protective enzyme systems it is not sufficient to test only changes e.g. of the C-O-methyltransferase (COMT), performed selectively in some centers. Other mechanisms of breast cancer development recognized by other research groups could supplement such screening methods in the future in order to identify women who should not receive MHT or should only receive it under special observation.

9 Conclusions for practical recommendations

The effectiveness of MHT results from the estrogen component for treatment of climacteric symptoms and prevention of osteoporosis and possible other preventive options like cardiovascular prevention (if MHT within a "Window of opportunity" early started), reduction of the incidence of diabetes mellitus and colon cancer. For women who have had a hysterectomy, the addition of progestogens should be avoided, as these essentially only cause risks, but are essential for women with uterus to avoid the risk of endometrial carcinoma. For this purpose, attention must be paid to adequate dosing of progestogens and at least 10–14 days of use. The progestogen can be added sequentially or continuously (daily). The endometrial effect should be monitored by means of bleeding behavior and vaginal sonography, especially when using progesterone, which has the lowest endometrial effectiveness. A progestogen challenge test can be carried out if necessary, and in case of endometrial

(suspected or proven) hyperproliferation, "hormonal curettage" is recommended using a synthetic endometrial effective progestogen in higher dosages for 10–14 days.

The most important study on MHT is the WHI trial. The risks identified in this study are VTE, risk of CAD, stroke and breast cancer, and must be considered, although WHI is fraught with significant problems, as in 60% late initiation of MHT and in 40% with the major risk factors for CHD and breast cancer (obesity, hypertension, smoking, etc.). Because the code was opened prematurely, there was no placebo control, and only one preparation that is only frequently used in the USA was tested. Therefore, observational studies for the choice of MHT must also be considered, according to which the use of transdermal estradiol (patches, gels, spray) can reduce the risk of VTE and stroke, and the use of progesterone or its retroisomer dydrogesterone can reduce disorders in lipids and glucose metabolism and especially the risk of breast cancer. The combination of these progestogens with estradiol, particularly transdermal estradiol, often is described as "golden standard", but other combinations may be preferred in special cases like antiandrogenic progestogens in clinical important situations of hyperandrogenism, e.g., PCOS. Alternatively the use of a levonorgestrel-IUD as the progestogen component may reduce progestogen-dependent risks and offer at the same time contraception, but often with longer bleeding problems and without the chance to get menstrual regulation, in contrast to sequential regimens of MHT. Cardiovascular prevention can be expected for any MHT if started early, but an increased risk of breast cancer cannot be

ruled out for any MHT. Therefore, a screening for the detection of hormone-dependent breast cancer mechanisms was developed in our own research, and likewise further research specifically to reduce the breast cancer risk is urgently recommended.

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Authors' contributions

Both authors contributed equally to planning and writing this review. Project leader of the research on mechanisms of breast cancer development was/is Alfred O. Mueck, whereas Xiangyan Ruan has been the corresponding author for most of the original papers published by our group on breast cancer research.

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Declarations

Ethics approval and consent to participate

As far as own studies are cited and/or reviewed in this article, all got approval by the ethical commission of Beijing Obstetrics and Gynecology Hospital, Capital Medical University. We conducted all animal studies in accordance with the guidelines approved by the Animal Experiments and Experimental Animal Welfare Committee of Capital Medical University, China (AEEI-2015–112). These guidelines comply with the ARRIVE guidelines carried out in accordance with the National Institute of Health guide for the care and use of laboratory animals (NIH Publications No.8023, 1978).

Competing interests

Both authors are strongly engaged in research of MHT. Alfred O. Mueck is Honorary President for Life of the German Menopause Society, Xiangyan Ruan is President of the Chinese Society of Gynecological Endocrinology affiliated to ISGE. Both authors are founders of the first official Menopause Clinic in China, treating now about 500 outpatients/day.

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