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Benefits and Risks of Menopausal Hormone Therapy

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Abstract

Menopausal Hormone Therapy (MHT) (estrogen/progestogen) is used to treat menopausal complaints and to prevent osteoporosis. Additional preventive benefits are reduction of cardiovascular disease, reduction of colon cancer, and perhaps also Alzheimer's disease, if started within a "window of opportunity", i.e. in perimenopause or within 6-10 years after menopause. Primary indication for progestogen addition is to avoid the development of estrogen-dependent endometrial cancer, i.e. addition not recommended in hysterectomized women. Two main schedules, sequential- or continuous-combined estrogen/progestogen regimens, are used. For optimizing menstrual regulation detailed recommendations are given.

The WHI-study demonstrated the main risks within a "worst-case scenario", start of MHT in old women with high risk for breast cancer and cardiovascular diseases, whereby only conjugated equine estrogens and medroxprogesterone acetate have been tested. Progestogen component is decisive for the breast cancer risk, which may be reduced using the progesterone or its isomer dydrogesterone. To reduce the risk of venous thromboembolism and stroke, transdermal estradiol (gels, patches) should be used, in free combination with progesterone or dydrogesterone as "golden standard" in patients with increased risks.

Own extensive experience in research also is included in this review. So within a "future outlook" we propose to push forward research for screening on mechanisms for hormone dependent development of breast cancer As both authors are working together in two universities, our research is done as cooperation project; we also had established the first official Menopause Clinic Center in China caring for 500 patients/day, the basis for practical recommendations included in this review.

Keywords: Menopausal hormone therapy (MHT); Estrogens; Progestogens; WHI-trial; MHT-regimens; MHT-indications; MHT-risks

Abbreviations: MHT: Menopausal hormone therapy; HRT: Hormone Replacement Therapy; HT: Hormone Therapy; WHI: Women's Health Initiative-trial; VTE: Venous Thromboembolism; CEE: Conjugated Equine Estrogens; MPA: Medroxyprogesterone Acetate; CHD: Coronary Heart Disease; NETA: Norethisterone Acetate; LNG: Levonorgestrel; GSM: Genitourinary Syndrome of Menopause; PGRMC1: Progesterone Receptor Membrane Component 1

Introduction

Menopausal Hormone Therapy (MHT) is defined as estrogen/progestogen-therapy in peri- and postmenopausal women for treatment of menopausal complaints including the genitourinary syndrome of menopause, to prevent osteoporosis, and to treat bleeding problems. Since these can be the indications also in young women, especially with POI (premature ovarian insufficiency) or with surgical menopause (bilateral oophorectomy), also the old term "Hormone Replacement Therapy (HRT)" is still used. Most specialized societies like the "International Menopause Society, IMS" or "North American Menopause Society, NAMS" [1,2] 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. The effective component is the estrogen component without relevant difference in the efficacy of the various MHT-preparations. In hysterectomized women all relevant guidelines recommend to use only estrogen [1-4], because the addition of progestogen can increase three of the main risks

observed in the Women's Health Initiative-trial (WHI), the most important study using MHT [5,6], i.e. breast cancer and stroke and, if combined MHT started longer than 10 years after menopause, also the risk of coronary heart disease [5]. 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 to this action by observing the bleeding patterns, 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 [1,3,4,7]. 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.

The following will describe the importance of WHI, especially for the evaluation of possible risks, which, however, needs to be supplemented with the results of observational studies. Further main topics of this review are 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 mechanism for breast cancer development on the basis of own research.

Benefits and Risks During MHT Based on WHI-Study

The WHI-trial is the most important study for MHT used in postmenopausal women, because it was a randomized placebo-controlled study comparing estrogen-only (n=5,310/5,429; 6.8 years) using conjugated equine estrogens (CEE) [5] with combined MHT (n= 8,506/8102; 5.2 years) (using medroxyprogesterone acetate (MPA) as the progestogen component) [6], in two study populations which were large enough for valid statistical analyses regarding the most important clinical endpoints. It must be stressed that the study populations had the most frequent risk factors for cardiovascular diseases and breast cancer like high age at the start of MHT, obesity, smoking, hypertension etc.) (Table 1) [5,6].

Table 1: Women's Health Initiative (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 (before or during the study)	48%	50%
Hypertension	48%	36%
further cardiovascular diseases *)	12%	22%

Note: *) Patients after deep vein thrombosis, pulmonary embolism, myocardial infarction, angina pectoris, by-pass surgeries, angioplasic surgeries, dyslipoproteinemia, diabetes mellitus etc. Modified according to the primary original publications WHI Investigators [5,6].

For 65% of the women, the start of MHT was beyond the age of 60, where we only in rare cases do recommend starting any MHT. Only one preparation (CEE, MPA) in one dosage (too high for the age group) was assessed: Therefore, we should not extrapolate the results to other preparations of MHT. Nevertheless, the WHI is the most important study for assessing the possible main risks in a "worst case scenario", i.e. late start in women with important risk factors.

Table 2 shows the main benefits and risks with the relative risks (hazard ratio, HR) and absolute 'excessive benefits or risks' [8]. Comparing both study arms can demonstrate the negative effect of the progestogen component: addition of MPA to CEE increased the risk of breast cancer and coronary heart disease (CHD) whereas these important risks were not significantly increased with estrogen-only. In a follow-up "per protocol analysis" (i.e., evaluating only women who certainly took the estrogen pills), there was a 30% decrease in breast cancer risk with estrogen-only, which was used in hysterectomized women [9], meaning that estrogen-only can prevent breast cancer development in postmenopausal women, even if they have an increased risk of breast cancer (see table 2). Later analyses stratifying the result by age showed large differences after comparing the younger with older age group (table 3) [10].

These results from the primary intervention studies have recently been confirmed in an 18-year- and 20-year follow-up analysis [11,12]. 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). So the difference in terms of the risk of breast cancer shown during the interventional phase of WHI persisted during

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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).

Table 2: Women's Health Initiative (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]	CEEb+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)	66
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)	66
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

Abbreviations: Ex B or R: 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.

Note: [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) (increase of M. Alzheimer risk not significant). Modified according to Kenemans P, Maturitas [8].

Table 3: Women's Health Initiative (WHI): Age Dependency of the Benefits and Risks (Number of diseases per 10,000 women per year and excessive benefit or risk, exBorR).

Combined Estrogen/Progestogen CEE/MPA	Age 50-59 years		Age 70-79 years	
	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	**Age 50-59 years**		**Age 70-79 years**	
	CEE/ Plazebo	exBorR	CEE/Plazebo	exBorR
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

Abbreviations: 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 to Barlow DH. Maturitas [10].

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The WHI-study not only showed us the risk if MHT is used within a "worst case scenario", i.e. in women with increased risk of breast cancer and cardiovascular disease (table 1), but also demonstrated an excellent beneficial effect for prevention of osteoporosis even in older women and in risk patients (table 2,3). The prevention of colon cancer (table 2,3) is also an important benefit, given that mortality and morbidity are higher than with breast cancer, which is often forgotten by our patients. Furthermore, other beneficial effects have been shown in the WHI and other studies, such as amelioration of lipid disturbances and prevention of diabetes mellitus, the most important reason for the development of coronary heart disease.

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 WHI-population should not be extrapolated to the benefits and risks of MHT if started early, like in the subgroup between 50-59 years [13]. 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.

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 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 (table 1). In addition, since about 40% have been obese (BMI > 30 kg/m^2), 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.

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 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.

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 coronary heart disease 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 increase blood flow, decrease the cardial afterload, avoid high blood pressure, etc.) and can achieve positive effects in lipids and glucose metabolism, i.e. cardiovascular prevention can be expected [14-16].

In risk patients the use of transdermal instead of oral estrogen can reduce the risk of venous thromboembolism [17-21] and stroke [16,22,23]. The use of progesterone or dydrogesterone (retro-isomer of progesterone) as progestogen component largely can avoid the increase of breast cancer risk during MHT [24-29]. However, the issue of hormone dependent breast cancer risk seems to be very complex, main topic of our and other research, as we already extensively have reviewed elsewhere regarding different hormone dependent mechanisms, including own research [30-32].

Optimizing MHT for Menstrual Regulation and Endometrial Protection

The primary indication to use a progestogen in MHT is endometrial protection, i.e. to avoid the risk of endometrial cancer during unopposed estrogen therapy. Adequate progestogen addition urgently is recommended in women with intact uterus. Progestogen is not generally indicated with estrogen therapy post hysterectomy [1-4].

Every type of combined MHT can be performed using one of the two main regimens – sequential-combined (i.e. first estrogen-only followed by estrogen + progestogen) or continuous-combined (i.e. daily estrogen plus progestogen). The sequential-combined regimen can be performed with or without a one-week break from hormones, although nowadays the regimen without a break is generally recommended to avoid recurrence of climacteric symptoms during the break and other estrogen-withdrawal symptoms such as menstrual migraine. For oral MHT, various "fixed combination" preparations are available. For sequential-combined MHT, the progestogen phase should be at least 10 days (preferably 12-14 days) per cycle to provide sufficient endometrial protection. Continuous-combined regimens only should be used in postmenopausal patients. [1,4,33] Figure 1 shows our practical recommendation for the use of MHT-regimens adapted to menopausal status.

Use of sequential MHT is often recommended in young women with bleeding problems, and is especially recommended in patients with premature menopause, starting after diagnosis and continuing up to the age of at least about 50 years. This MHT needs higher estrogen doses or transdermal estradiol (gels, patches) with at least 50µg/day released out of the preparations via skin into the systemic circulation [33,34].

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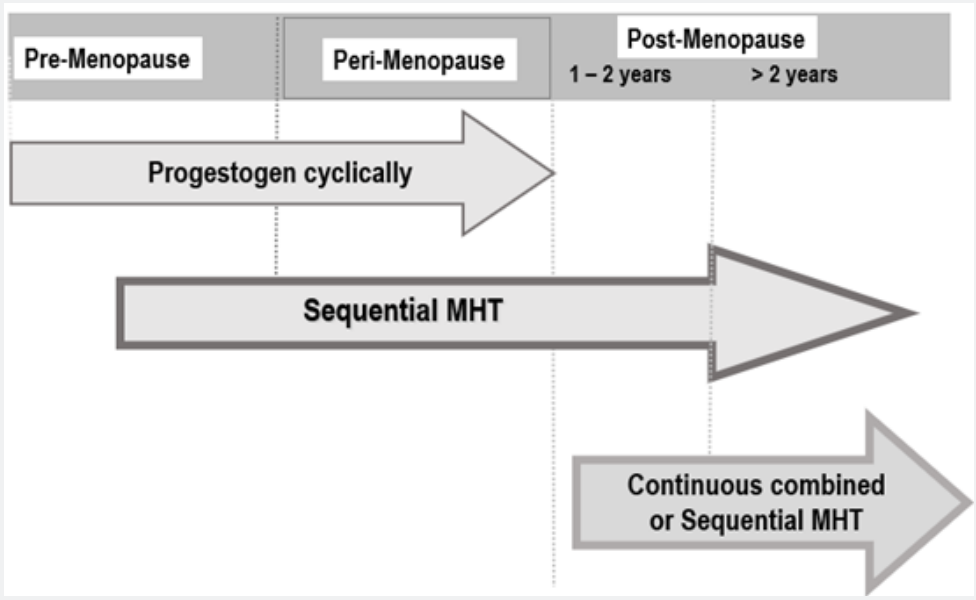

Figure 1: Practical recommendation: MHT-regimen adapted to menopausal status.

The regular withdrawal bleeds during sequential MHT should best occur during the hormonal pause if MHT with a hormonal pause, or at the beginning of the estrogen phase with regimens which do not have a hormonal pause. However, bleeding can often occur about 1-3 days earlier, but should not be at the beginning of the progestogen phase, because this would be a sign of insufficient endometrial efficacy of the progestogen. If such early bleeding occurs, the progestogen dose should be increased, or the progestogen type should be changed. Mid-cycle bleeding is usually breakthrough bleeding, which indicates insufficient endometrial proliferation, and the estrogen dose should be increased.

Continuous combined HRT is defined as using estrogen and progestogen on a daily basis. The aim of this regimen is to obtain and maintain endometrial atrophy without any bleeds. Continuous combined regimens should not be used in perimenopausal patients, because severe bleeding problems can often occur. It is important to note that no bleeding should occur with continuous combined regimens. However, 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 does not require further invasive diagnostic procedures (because all these procedures have other risks). However, if bleeding occurs 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) [35-37].

For practical use approved fixed combination-products may have some advantages if the choice is oral MHT. Alternatively, a "free combination" offers the possibility for the individualization of MHT, provided that the patient shows good compliance with the use of two preparations. When using transdermal estradiol as gels, patches or as spray, any progestogen must be added separately as an oral preparation, with two exceptions: transdermal norethisterone acetate (NETA) and transdermal levonorgestrel (LNG) are available as fixed combinations in so called "combi-patches". However, because adhesion problems and skin irritation are common with these patches, and also because of bleeding problems, those "combi-patches" are not often used in clinical practice.

Appropriate dosing regimens for free combinations using the different progestogens dependent on the estradiol dosages within sequential or continuous combined therapy are provided in table 4, according to the literature and own clinical experience [37].

A special continuous combined "free combination" is 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 20µg levonorgestrel/day are used [38,39]. 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, but, however, cannot be used as contraception.

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Table 4: 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 Continuous	200 mg 100 mg	200-300 mg	300-400 mg
Medroxyprogesterone acetate	Sequential Continuous	5-10 mg (2.5-)5 mg	10-20 mg 5-10 mg	20 mg
Chlormadinone acetate	Sequential Continuous	2-4 mg (1-)2 mg	4 mg 2-4 mg	4-6 mg
Cyproterone acetate	Sequential Continuous	1 mg 1 mg	2 mg 1-2 mg	3-5 mg
Dydrogesterone	Sequential Continuous	10 mg 5(-10) mg	10-20 mg 10 mg	20 mg
Norethisterone acetate	Sequential Continuous	1 mg 0.5 mg	1-2 mg 1 mg	2 mg
Dienogest	Sequential Continuous	2 mg 2 mg	2-4 mg 24 mg	4 mg
Levonorgestrel (intrauterine)	Continuous	20 µg	20 µg	20 µg

Note: 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 0.3/04 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.

Note: For gels, patches, spray, these are the not the dosages which are within the various available preparations. For example gels with (according to the package insert) recommended 1.5g (= 1,500 µg!) daily application or patches containing 3 - 4 mg do release only about 30 - 50µg 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. Modified according to Mueck AO, Römer T [37].

Endometrial Monitoring During Use of Miconized Progesterone

There is ongoing discussion about the endometrial safety using micronized 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 elicits 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 besides progesterone 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 [40]. More carefully conducted studies with well-reported dosing of progesterone have not demonstrated this risk, such as the prospective randomized placebo-controlled study PEPI for sequential [41] and the REPLENISH-trial [42] 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. 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 4, may be still the best choice for risk patients, and in view of many experts still the "golden standard" in MHT [43,44].

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

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other day [40]. The stronger effect when applied vaginally is based on the fact that more progesterone is introduced into the endometrium by an "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 [45].

Benefits of Optimized MHT: Efficacy in Treatment and Prevention

All forms of MHT-preparations with systemic activities (orally and transdermally) have some form of beneficial effects for almost all symptoms and diseases known arising during or after the menopausal transit. Table 5 summarizes the benefits of optimized MHT, whereby it must be differentiated between 1) currently officially listed indications, which more or less are labelled within the package insert of most MHT-products; 2) proven additional preventive benefits, and 3) presumed additional preventive benefits. Additional preventive benefits with reduction of the risk of clinically very important diseases only can be excpected in case of diffentiated and individualized use of MHT and considering other important rules like early start within a "window of opportunity" (especially for prevention of cardiovascular diseases and dementia) [1,4,14,15,33,44]. The rational of this "window" for the first time was based on the famous research of TB Clarkson and his group investigating in cynomolgus monkeys how timing of estrogen therapy influences cardiovascular preventive effects [15]. At least four metanalyses based on more than 40 observational studies confirmed this cardiovascular preventive concept for MHT in peri- and postmenopausal women (reviewed e.g. in [46].

Table 5: 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)	Coronary heart disease Alzheimer's disease Various atrophic-degenerative diseases (skin, mucous membranes, connective tissue), rheumatic diseases Certain forms of schizophrenic psychoses Lung cancer?

There especially is a benefit for treatment of climacteric symptoms, genitourinary syndrome of menopause (GSM), prevention of osteoporotic fractures, prevention and treatment of uterine bleeding problems, prevention of coronary heart disease (if the MHT is early started in perimenopause or early post menopause), prevention of colon cancer and prevention of Alzheimer disease (if early started) [1,4,33,44]. Even a reduction of breast cancer, which has been shown with CEE in the WHI (estrogen-only arm) and has been seen also using E2 in MHT [28,47]. So prevention of breast cancer also can be listed in the table of presumed benefits for the use of E2-only which is possible in hysterectomized women (table 2,3), but dependend on the population an increased risk cannot be excluded during long-term estrogen-only therapy [1-3,25].

Even differentiated and individualized MHT is necessary to get those benefits, there are regarding efficacy no qualitative differences between the various forms of MHT. However, different are possible risks, especially comparing oral and transdermal estrogens: Use of transdermal E2 (gels, patches, spray) can reduce the risk of venous thrombosis in contrast to all oral estrogens [17-21]. So in patients with increased risk of venous thrombosis the use estradiol transdermal urgently is recommended [1,4,7,31,33,44]. Regarding this important difference between oral and transdermal application it should be mentioned, that according to own research the risk of venous thromboembolism is very rare in China, but high in Western countries [48].

Contraindications and Non-Hormonal Alternatives

According to the official labelling of MHT-products there is a large list of contraindications, summarized in table 6. The contraindications are the same for all MHT-preparations (and even mostly the same compared to hormonal contraceptives) according

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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 venous thromboembolism will get prescribed oral estradiol instead of transdermal estradiol and would suffer from a pulmonary embolism, this strong prescription mistake would have even forensic consequences.

Table 6: Contraindications for the use of MHT.

Absolute contraindications **)	Unexplained vaginal bleeding, endometrial hyperplasia breast cancer, endometrial cancer. endometroid ovarian cancer
(listed contraindications)	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	Asthma, multiple sclerosis, otosclerosis, melanoma, liver tumours

**) Exceptions must be justified in a forensically verifiable manner.

***) Treatment possible with individualized differentiated MHT and close monitoring.

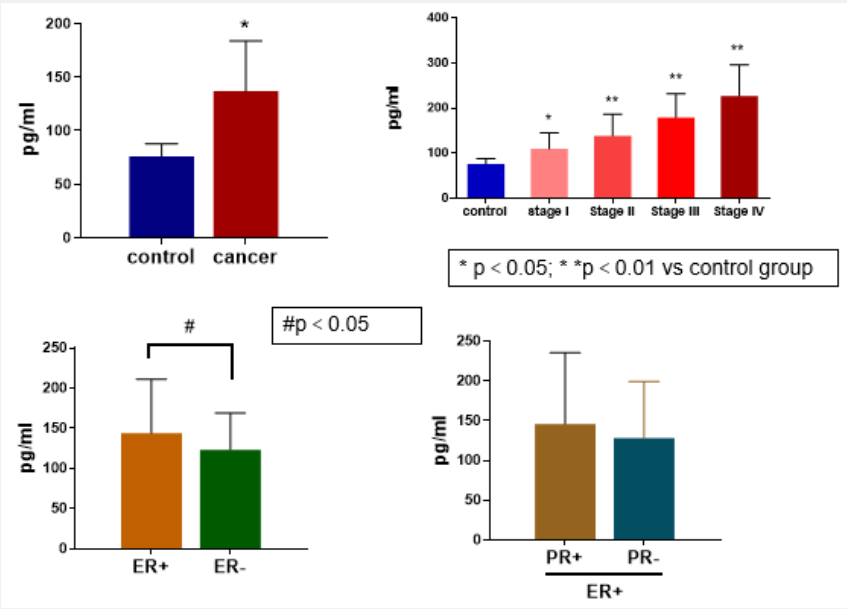

Figure 2: Correlation of PGRMC1 blood concentrations with clinical tumor characteristics.
Note: Significant increase of PGRMC1 blood concentrations dependent in breast cancer patients dependant on staging. Modified according Ruan X [63].
Figure 2: Correlation of PGRMC1 blood concentrations with clinical tumor characteristics.

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For patients with contraindications several non-hormonal derived drugs have been recommended (e.g. [1, 49], 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 [50,51]. But using special forms of "Traditional Chinese Medicine" in the hands of Chinese experts have shown good efficacy for treatment of menopausal complaints and also for menstrual regulation [52], included the use of acupuncture according to also own experience in thousands of patients [53].

Regarding herbal products we for example have good experience using "black cohosh (Cimicifuga racemosa)" [54]. These preparations are an important alternative for patients who have contraindications for MHT, because their action is not via estrogen receptors but via effects in the serotonin transmitter system. For this reason, we have concluded that black cohosh also can be used for the treatment of climacteric symptoms in patients with hormonal-dependent cancer such as breast cancer and endometrial cancer [54]. The same is true for the use of a new herbal alternative, a "purified and specific cytoplasmic pollen extract" [55], with which we have been able to demonstrate that this extract does not stimulate breast cancer cells [56]. With both alternatives, black cohosh and the pollen extract, efficacy for the treatment of climacteric symptoms is quite good, but less than with any MHT, and both do not have osteoprotective effects and no preventive effect on the cardiovascular system or against colon cancer.

Outlook: Screening for Mechanisms for Development of Hormone Dependent Breast Cancer

The most important risks associated with any form of MHT 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 coronary heart disease (CHD) and stroke, which can be reduced by early initiation of MHT; and 3) an increased risk of breast cancer. Regarding the risks 2) and 3) the possible negative impact of the progestogen component has been well demonstrated in clinical studies as reviewed elsewhere [57,58]. In most studies the synthetic progestogens MPA or norethisterone (acetate) 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 [24-29,57].

Since an increased risk of breast cancer may not be ruled out with any MHT, even not during long-term use of progesterone or its retro isomer dydrogesterone [25], 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 [59]). For this research we have been encouraged by Editorials in relevant journals with the discussion that our experimental results may explain the increased risk in the WHI study [60,61], asking "Can the increase in breast cancer observed in the estrogen plus progestin arm of the Women's Health Initiative trial be explained by progesterone receptor membrane component 1 (PGRMC1)?". 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 expression of those receptors 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 [62], we were recently able to detect in the blood as well [63], and we could show that screening on these receptors is comparable predictive like other already known tumor markers [63]. Figure 1 demonstrates the results of such a study [62].

This is one example from own research. However, screening for already recognized other mechanisms of breast cancer developments [30] may in future be a chance to detect women of higher risk, e.g. screening for potential genotoxic estrogen metabolites, as we recently have published elsewhere [32] suggested already decades ago in ''Science" [64]. Those future screening concepts to avoid at least breast cancer development based on known mechanisms can identify women who should not receive MHT or should only receive it under special observation.

Conclusion for Optimizing MHT

The first conclusion is to try to start every MHT within a "window of opportunity" (i.e. during perimenopause or within 6-10 years after menopause) to get the most important benefit, i.e. to prevent cardiovascular diseases, which are the most frequent reason for mortality and morbidity of women (like for men). Secondly, we should try to reduce the risk of breast cancer mostly feared by women and doctors. For this, research should develop methods to screen for women who are of higher risk of breast cancer development.

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 venous thromboembolism and stroke, and the use of progesterone or its

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retro isomer dydrogesterone can reduce disorders in lipids and glucose metabolism and especially the risk of breast cancer, at least for treatment up to eight years. 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, in contrast to regimens of MHT.

Until now any forms of transdermal progesterone-preparations do not seem to elicit sufficient endometrial efficacy. Recently also fixed oral E2/progesterone-preparations (capsules) have been developed. However, cardiovascular risks like venous thromboembolism, stroke and coronary heart disease (for start of MHT in older women) cannot be excluded whenever estrogens are used orally. Thus, that new option for MHT in our view cannot replace the use of transdermal estradiol to reduce these risks. So, we still recommend transdermal estradiol plus additional free combination of progesterone or dydrogesterone or levonorgestrel-IUD especially for risk patients although for the daily clinical practice in women without those risks the available oral fix-combinations may increase patient's compliance for the agreement to use any indicated MHT.

Conflict of Interest

Both authors are strongly engaged in research of MHT, being supported by various companies. 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.

Authors' Contribution

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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